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Review

MicroRNA: A signature for cancer progression

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ABSTRACT

MicroRNAs (miRNAs) are a group of small non-coding RNAs that post-transcriptionally control expression of genes by targeting mRNAs. miRNA alterations partake in the establishment and progression of different types of human cancer. Consequently, expression profiling of miRNA in human cancers has correlations with cancer detection, staging, progression, and response to therapies. Particularly, amplification, deletion, abnormal pattern of epigenetic factors and the transcriptional factors that mediate regulation of primary miRNA frequently change the landscape of miRNA expression in cancer. Indeed, changes in the quantity and quality of miRNAs are associated with the initiation of cancer, its progression and metastasis. Additionally, miRNA profiling has been used to categorize genes that can affect oncogenic pathways in cancer. Here, we discuss several circulating miRNA signatures, their expression profiles in different types of cancer and their impacts on cellular processes.

1. Introduction

Cancer is a complex genetic defect comprising structural and expression abnormalities of coding and non-coding transcripts. The first indication of miRNAs correlation with cancer was revealed in 2002 through detection of recurrent deletions in a miRNA-coding region in half of patients with B cell chronic lymphocytic leukemia [1]. Since that time, it has been shown within the scientific community that miRNAs dysregulation is highly influential and partakes in cancer development and progression [2]. Moreover, several miRNAs have been detected that have tumor suppresser or oncogenic roles [3–5]. It is now clear that the genomic complexity of the neoplastic cells is much more than estimated. After these significant findings, the characterization and cloning of small, non-coding RNAs with ~22 nt length has led to the recognition of more than 1000 miRNAs. miRNAs play fundamental regulatory roles in shaping cellular activity, including development, differentiation, proliferation, apoptosis, and genomic stability [6] through specific base-pairing with target transcript and/or protein molecules, and transcriptional and post-transcriptional regulation of their expression [7].

GENCODE data (v.29) has listed around 2600 mature miRNAs encoded by 1872 annotated miRNA precursor genes in human [8]. Functions of many of these miRNAs are still unknown [9]. A single miRNA might bind with up to hundred different transcripts [8,10]. Moreover, a specific mRNA may attach to various miRNAs, either simultaneously or in a circumstance-dependent manner [11]. miRNAs have direct contribution in oncogenesis in diverse tissues since they function as tumor suppressors (miR-15a and miR-16–1) or oncogenes (miR-17–92 cluster and miR-155) [12,13]. Moreover, miRNAs have been regarded as markers for genetic susceptibility to cancers [14,15]. Molecular analysis showed that the genomic aberrations such as chromosomal rearrangements, deletions, and mutations or genomic amplifications impact on the activity of miRNAs [13].

In addition to their effects in the cellular functions in cancer cells, miRNAs can regulate function of other cells in the tumor niche. Extracellular miRNAs can affect intercellular communications cooperating with stromal cells and constituents of the extracellular matrix to create a suitable microenvironment for cancer cells to grow and escape from immune responses [16]. For instance, miR-200c decreases expressions of PTEN and FOG2, inducing PI3K/Akt cascade and leading to amassment of myeloid-derived suppressor cells and inhibition of immune

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response in the tumor milieu [17]. Moreover, macrophages have been shown to secrete miRNA-containing exosomes to enhance invasiveness of breast cancer cells. Notably, miR-223, a miRNA specific for interleukin-4-induced macrophages has been among these miRNAs [18]. In addition, exosomal transfer of miR-144 and miR-126 has an important role in the establishment of a new metabolic system in favor of cancer progression [19].

2. Biogenesis of miRNAs

The mechanism of biosynthesis of miRNA is schematically presented in (Fig. 1). It involves a complex protein process in which the Argonaute protein family members, RNA pol II, and the RNase III enzymes (Drosha and Dicer) participate [7]. After being transcribed by RNA pol II, the long precursor (pri-miRNA) is used to produce another transcript with hairpin structure an approximately 70 nt, namely the precursor-miRNA (pre-miRNA) [20,21]. The pre-miRNA then experiences additional processing steps catalyzed by Dicer [22,23]. This cleavage event results in production of an approximately 22-nt miRNA duplex comprising of mature miRNA [24]. Later, the mature double-stranded RNA binds to Argonaute proteins producing RNA-induced silencing complex (RISC) [25] which subsequently controls the translation of target mRNA with complementary sequences in the 3′ untranslated region (UTR). miRNAs binding with other regions, including open reading frame (ORF) or 5′UTR of the mRNA and gene promoters have been described as well [26–29]. A schematic illustration of miRNA biogenesis can be seen in Fig. 1.

3. Mechanisms of abnormal expression of miRNA in neoplasms

Over the last decades, dysregulation of miRNAs expression has been observed in diverse neoplams. In spite of significant progress in understanding and knowing the basic mechanism of miRNA biosynthesis, less is recognized about the mechanisms that control miRNA biogenesis and how this process might be dysregulated in the oncogenic process. According to the finding of the recent studies, the mechanisms of miRNA dysregulation primarily involves the amplification or deletion of miRNA genes, abnormal activity of transcription factors, epigenetic dysregulation, and defects in the genes in the miRNA biogenesis pathway [13]. Furthermore, competitive endogenous RNAs (ceRNAs) might decrease intracellular miRNA level.

3.1. Amplification or deletion of miRNA genes

miRNAs are encoded in various regions of the mammalian genome. Around half of miRNAs are transcribed from non-protein-coding regions, whereas approximately 40% reside in the introns of protein-coding genes [30,31]. Intronic miRNAs are usually transcribed with their host genes, yet the pattern of intergenic miRNAs is less understood. Numerous miRNAs are located in neoplasm-associated genomic regions or common breakpoints adjacent to fragile sites [32], and in other genomic sites which harbors cancer-associated rearrangements.

The earliest discovery of miRNAs role on cancer has reported that two clusters of miRNA genes, miR-15a and miR-16a are located within the 13q14.3 region which is lost in chronic lymphocytic leukemia (CLL) and that both genes are frequently deleted in most of CLL cases [1]. Moreover, the loss of both miR-15 and miR-16–1 genes is highly correlated to CLL, and promotes the overexpression of BCL2 and ROR1 [33–35]. Therefore, loss of miRNAs resulted from chromosomal deletion or rearrangements may cause oncogenesis. Further comprehensive analysis revealed that both miR-143 and miR-145 genes located on chromosome 5q33 region are often deleted in lung cancers, resulting in reduced expression of both miRNAs [36]. In particular, the miR-17–92 cluster on a translocation site has been overexpressed in T-cell acute lymphoblastic leukemia and induced lymphomagenesis in vivo [37]. Lin Zhang et al. identified high-frequency genomic abnormalities in miRNA loci in 227 samples of human breast cancer, ovarian cancer, and melanoma [38]. Overall, these results indicate that unusual expression of miRNA in cancer cells might be resulted from amplification or deletion of particular genomic sites of miRNA genes.

3.2. Regulation of miRNAs transcription

Expression of miRNAs is closely regulated via various transcription factors, so aberrant expression of miRNA in tumors may be resulted from dysregulation of some major transcription factors, including p53 and c-Myc. Several studies have shown conclusive indications that changes in transcriptional protein activators or suppressors lead to abnormal pri-miRNA transcription in human cancers. As an example, genes encoding miR-34a, miR-34b, and miR-34c are directly controlled by the p53, indicating the impacts of the functional p53 in determining expression of miR-34 in neoplastic cells [39,40]. p53 is upregulated as a response to DNA damage and oncogenic stress, and controls the transcription of miR-34, which triggers apoptosis, cell cycle arrest, and cell senescence in different types of cancer [41]. miR-145 is also transcriptionally activated via over-expression of p53 to promote apoptosis [42–45]. RAS-responsive element-binding protein 1 (RREB1) downregulates miR-143/145 levels and promotes tumorigenesis [46]. p53 also controls expression of a variety of miRNAs, including miR-107 [47], miR-1246 [48], and miR-605 [49,50]. miR-145 expression is also affected by other transcription factors, such as beta-catenin/T cell factor 4 (TCF4) [51], C/EBPβ, PPARγ, BRCA1 DNA repair associated (BRCA1) and forkhead box O (FoxO) [52–55] in human tumors. The c-myc proto-oncogene encodes a protein that controls the transcription of various genes, including non-coding and protein-coding genes [56,57]. Over-expression of c-myc is a critical step in various cancers and is correlated with abnormal expression of several genes including miRNA genes [58,59]. The oncogenic c-Myc protein promotes expression of miR-17–92 cluster by binding to E-box in the promoter of miR-17–92 [60]. c-Myc inhibits transcriptional activity of tumor-suppressor miRNAs such as miR-6–15a-20–29 and let-7 [61]. Moreover, recurrent amplification of 13q31-q32 locus, which has the miR-17–92, is frequently found in lymphomas harboring MYC rearrangements, indicating that the miR-17 cluster and c-Myc may work together to promote aggressive cancer development [62]. In hepatocellular carcinoma (HCC), c-Myc attaches to the conserved regions of miR-363–3p or miR-148a-5p promoter genes and suppresses their expression [58]. In turn, miR-363–3p destabilizes Myc through the direct binding and inhibiting ubiquitin-specific protease 28, whereas miR-148a-5p directly binds and suppresses Myc expression [63]. Suppression of miR-363–3p or miR-148a-5p promotes hepatocellular tumorigenesis by inducing G1 to S phase progression. In addition to p53 and c-Myc, which are two already studied transcriptional factors, more proteins have been discovered as transcriptional factors that control miRNA expression. For example, Mef2c which motivates the proliferation of myeloid progenitor, is influenced by miR-223, and the genetic ablation of Mef2c transcriptional factor advantageously inhibits the progenitor expansion and amends the neutrophilic phenotypes [64,65].

3.3. Epigenetic control of miRNAs

An eminent characteristic of cancer is epigenetic alteration. DNA methylation and histone tail modifications change chromatin structure. Epigenetic is known as meiotically and mitotically heritable gene expression changes that do not include DNA nucleotide alterations. The utmost frequent epigenetic modifications are methylation of DNA at the 5-carbon of the cytosine and modification of histone tails (histone acetylation and methylation) [66,67], which are identified to have major impacts on the expression of human genes. Methylation of histone H3 lysine 9 is an important event in epigenetic control of gene expression and might be stimulated by DNA methylation [68]. Histone methyltransferases have been shown to interact with other enzymes that

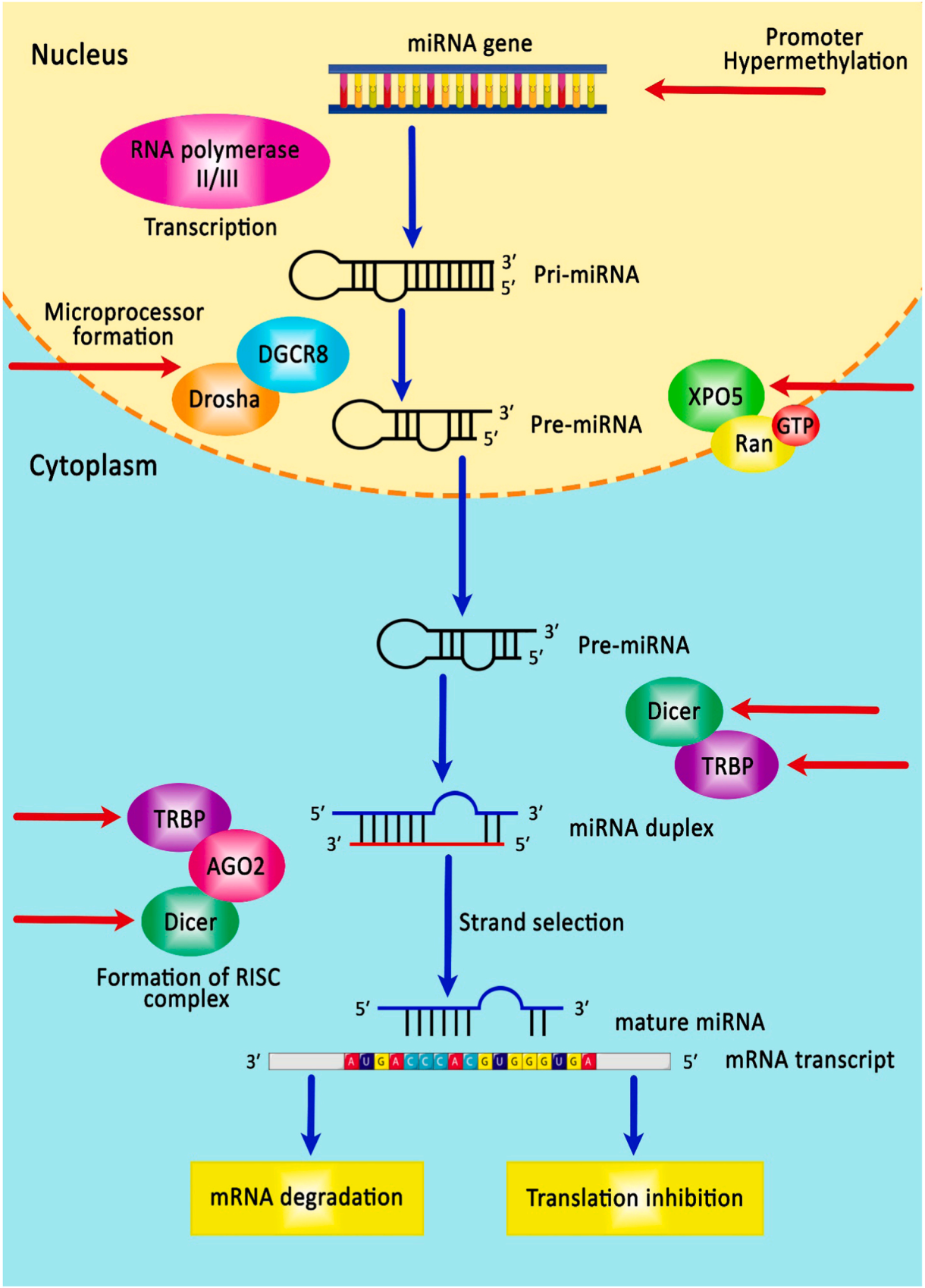

Fig. 1. Biogenesis of miRNAs has several steps: (1) Transcription by RNA polymerase II resulting in the production of long primary miRNA transcripts with diverse sizes (pri-miRNA). Within the nucleus, pri-miRNA is cleaved by Drosha RNase III enzyme creating a hairpin configuration known as pre-miRNA. (2) Export of pre-miRNA into the cytoplasm by exportin 5 and its processing by Dicer. (3) Creation of the transient 19–24 nucleotide duplex. Only the mature miRNA from the miRNA duplex is integrated into RISC. (4) The mature miRNA directs RISC to degrade mRNA or prompt translational suppression or translational activation.

modify epigenetic marks on DNA or histones [68]. Disruption of epigenetic mechanisms results in aberrant expression of miRNAs in cancer cells [69,70]. Fig. 2 depicts the DNA-methylation patterns of miRNAs in normal and tumor cells.

3.3.1. DNA Methylation

Methylation of DNA typically happens in all vertebrate cells at carbon-5 of cytosine ring in CpG dinucleotides. This process is mediated by DNA methyltransferase (DNMT) family, using S-adenosyl-methionine (SAM) as methyl-donor. Methylation of CpG human promoter genes are usually inhibited, while unmethylated CpG promoters can be expressed. Studies have shown that numerous miRNAs target each mRNA, and it is predicted that up to 30% of human protein-coding genes are controlled by miRNAs [73]. Similar to protein-coding genes, miRNAs are prone to epigenetic alterations. For example, Zhenhai et al. has discovered that intronic miR-340–5p expression was epigenetically downregulated by promoter DNA methylation of its host gene in multiple myeloma [74]. Saito and his colleagues showed that 17 out of 313 human miRNAs in T24 bladder cancer cells are over-expressed more than 3-folds after concurrent treatment with suppressors of DNA methylation of DNA and histone acetylation. miR-127 is one of these miRNAs which is located in a CpG island and its expression is extremely promoted in the tumor cells after treatment with 5-Aza-2′-deoxycytidine in combination with 4-phenylbutyric acid, decreasing levels of its target BCL6 proto-oncogene [75]. These findings show that both DNA demethylation and histone deacetylase inhibition could induce the expression of such types of miRNAs. Another study stated that DNA hypomethylation causes a release of miR-124a silencing in colorectal cancer cell lines through transcriptional inactivation by CGI methylation [76]. miR-34b/c and miR-148a also undergo certain hypermethylation-associated silencing in metastatic cell lines from head and neck cancer, colon cancer and melanoma cells. Furthermore, hypermethylation-associated silencing of these miRNAs reduced tumor growth and inhibited metastasis formation in vivo [77]. Hyper-methylation of miR-124, miR-125, miR-126, miR-127, miR-148a, miR-193a, miR-132, miR-133a-3p, miR-137 and miR-34b/c has been found in breast cancer cells [78–82]. In addition, let-7a, miR-9, miR-10b, miR-152, miR-200, miR-195/497 family, and miRNAs at the DLK1-DIO3 imprinted locus harbor similar epigenetic marks [83–85]. Down-regulation through methylation process of some miRNA such as miR-149 was described in chemoresistant breast cancer patients [86]. Furthermore, a number of miRNAs which suppress proliferation, invasion, and migration of cancer cells, were downregulated due to promoter hypermethylation in different types of cancer. Among these miRNAs are let-7a, miR-9, miR-34b/c, miR-338–3p, miR-596, miR-125a-5p, miR-375, miR-27b-3p, miR-495–3p, miR-490–3p and miR-124a in gastric cancer [87–97], let-7a, miR-9, miR-124 s, miR-125a-5p, miR-192, miR-615–5p, miR-1247, miR-142–3p, miR-148a, miR-132, miR-200, miR-152, miR-17 and miR-92 in pancreatic cancer [98–109], miR-9, let-7a, miR-191, miR-203, miR-335, miR-137, miR-142, miR-148a, miR-375, miR-195, miR-183, miR-497, miR-124, miR-125, miR-378, miR-639 in HCC [110–120], and let-7a, miR-107, miR-203a, miR-1258, miR −9, miR-107, miR-124–3p, miR-125b-5p, miR-127–5p, miR-129–5p, miR-130b, miR-132–3p, miR-137, miR-148a-3p, miR-339–3p, miR-375, miR-34a, miR-203a, miR-34b/c, miR-191–5p, miR-193a-5p, miR-193a-3p, miR-196, miR-508–3p, miR-424/503 cluster in ovarian cancer [121–132].

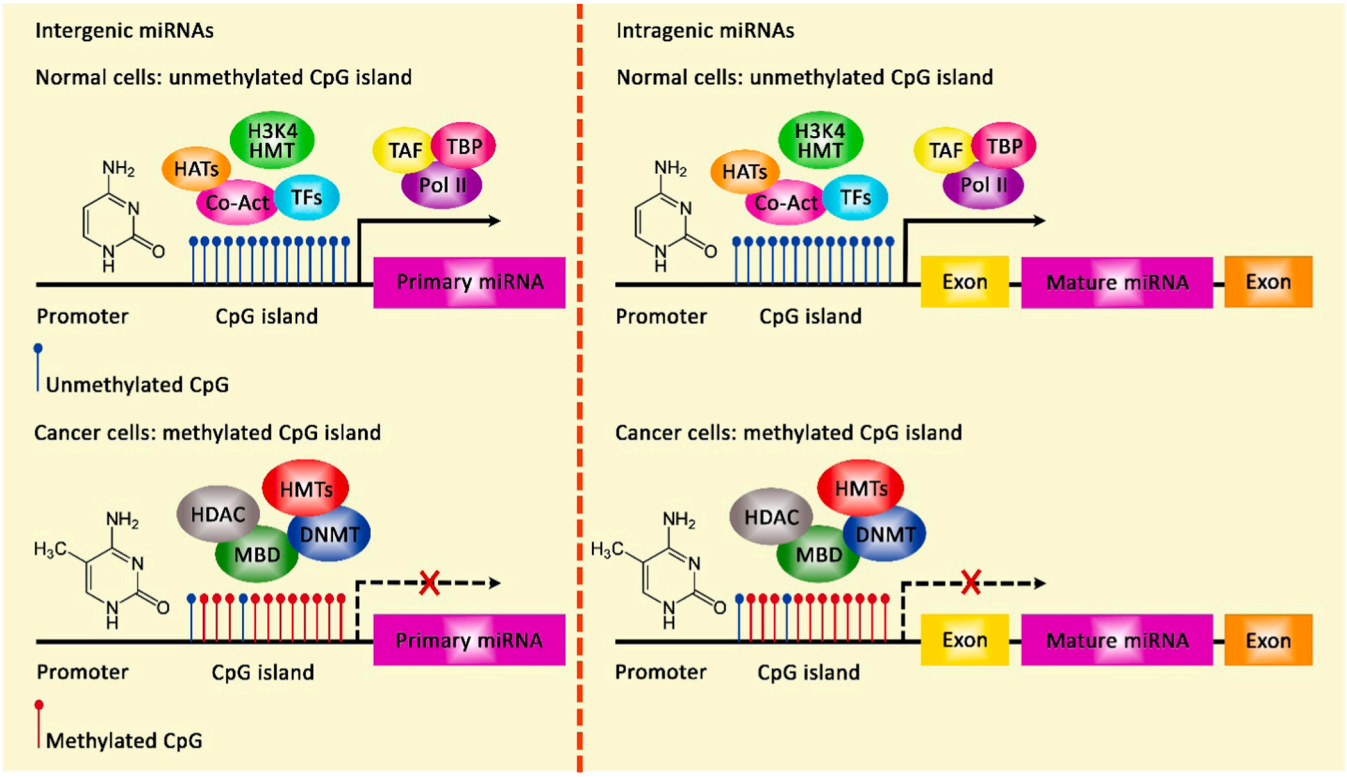

Fig. 2. A schematic model of DNA methylation-dependent miRNAs in normal & cancer cells. Aberrant promoter DNA methylation pattern in tumorigenesis. In normal cells, CpG dinucleotides (lollipops) of promoter intergenic or intragenic miRNAs associated CpG island are usually unmethylated (blue lollipops) which could lead to a euchromatin histone configuration allowing availability of TFs, HATs, HMT and RNA polymerase complex, for miRNA transcription, and thereby transcription could occur. Whilst, in tumor cells, promoter of intergenic or intragenic miRNAs associated CpG islands is aberrantly hypermethylated (red lollipops) via DNMT that associated with recruitment of HMT, MBD and HDAC, leading to a compact chromatin configuration, and thereby availability of transcription complex is blocked, resulting in miRNA silencing. TF: Transcription factor; Pol II: RNA polymerase II; HDAC: Histone deacetylase; MBD: Methyl-CpG-binding domain protein; TAF: TBP-associated factor; TBP: TATA-binding protein; Co-Act: Co-activator; HMT: Histone methyltransferase; DNMT: DNA methyltransferase; HAT: Histone acetyltransferase [71,72]. (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)

It has been shown by numerous studies that there is a significant change in the expression profile of the miRNA not just in tumor samples but also in the blood and urine of patients with bladder neoplasm [133, 134]. Bladder carcinogenesis and chemotherapy resistance are closely related to miRNA expression dysregulations [135]. Various miRNAs such as let-7, miR-145, miR-152, miR-10a, miR-129, miR-148, miR-193, miR-935, miR-137, miR-126, miR-200 and miR-205 showed significantly higher methylation levels in bladder cancer patients [136–144]. miR-137, miR-124, miR-2, miR-3 and miR-9 were specifically methylated in urine specimens of bladder cancer [137,138]. Recent studies interpreted that aberrant DNA methylation usually leads to dysregulation of miRNAs in cancer, and methylation pattern of certain miRNAs may be an important marker for cancer diagnosis and prognosis. Such dysregulation of miRNA signature results in genome-wide epigenetic abnormalities [145]. For example, hypermethylation of DNA sequences, histone modifications, and abnormal miRNA expression patterns have been regarded as three main epigenetic alterations that contribute in leukemia progression [146].

Promoters of let-7a, miR-9, miR-124–3p and miR-125 genes are silenced by aberrant CpG methylation in breast, ovarian, gastric, lung, pancreatic, and bladder cancers. Silencing of miRNA genes allows up-regulation of essential products of the oncogene, such as epidermal growth factor (EGF) and cyclin G1 (CCNG1) [147], which lead to progression of tumor and cancer invasiveness.

Hyper-methylation in the promoter region of miRNA-137 has been found in more than ten different types of cancer, which is contributed to transcriptional repression of miRNA-137 and affects the regulation of various cellular processes in tumor cells, such as remodeling of the chromosome by direct targeting of the EZH2 [148,149], cell cycle progression by targeting Cdc42 and Cdk6 [150], metabolism of tumor glutamine by targeting ASCT2 [151] and TRIM24 [152], chromatin remodeling by targeting LSD1 [153].

Tumor-suppressor miR-34 gene is also hypermethylated at the CpG site in the promoter region in numerous tumors, and its silencing has affected various cellular process by targeting NOTCH1 [154] and CD44 [155]. This process also affects cellular senescence via modulation of telomerase activity through targeting FoxM1 and c-Myc [156,157], and apoptosis by direct targeting BCL2 protein apoptosis regulator [158].

3.3.2. Histone modifications

The key protein components of chromatin are histones, a series of small, highly conserved proteins. Histone tail methylation and acetylation are the two main modifications of histone proteins in chromatin that play a key role in its regulation in response to different cellular signals. The main biological processes including DNA replication, gene expression, and repair of DNA damage are regulated by histone proteins modifications, which occur at specific residues on histone N-terminal tails [159]. Histone deacetylation gave rise to a more compact chromatin state and inhibited gene transcription, while acetylation of lysine-tails in histone protein was associated with a more relaxed chromatin structure and activation of gene transcription [160]. Scott et al. were the first group who showed the evidence of miRNA deregulation due to the modification of histone proteins in tumor cells in 2006. They found 27 aberrantly expressed miRNAs in breast cancer after treating SKBr3 breast cancer cells with an HDACs inhibitor [161]. Other investigators have shown that HDAC inhibitor affects miRNA expression in different types of cancer [69, 160–164]. Due to the overexpression of HDACs (HDAC1, HDAC2, and HDAC3), miR-29b, miR-15a, and miR-16 are epigenetically repressed in mantle cell lymphoma (MCL) and CLL. Indeed, HDAC inhibition restores the expression of miR-29b, miR-15a, and miR-16 in CLL cells, and was associated with declining levels of MCL-1 and triggered CLL apoptosis [165].

Furthermore, in HCC cells, overexpression of histone deacetylases (HDAC1–3) decreases expression of miRNA-449. miR-449 attaches to c-MET mRNA to decrease its levels, reducing proliferation, and promoting apoptosis of liver cancer cells [166]. Notably, histone acetylation, in some settings, is involved in oncomiR activation in cancer. For instance, in HCC, miR-224 is commonly overexpressed. It has also been reported that miR-224 expression is positively associated with histone acetylase EP300 protein in HCC patients [167].

3.4. Abnormal function of genes in the biogenesis of miRNA pathway

In addition to genomic alterations, transcription factors, and alterations of epigenetics mechanisms, defects in the miRNA biogenesis system influence the expression of miRNA and enhance oncogenesis. The altered expression of Dicer and Drosha, two main enzymes in the miRNA maturation is linked to down-regulation of miRNAs in numerous kinds of human cancer including breast cancer [168,169]. *In vitro* and genetically modified human cell lines proved that DICER1 and DROSHA mutations affect miRNA processing via several routes.

Mutations in DICER1 generally impair miRNAs biogenesis from the 5'-arm of pre-miRNA hairpins, whereas DROSHA mutations impede miRNA processing via a dominant-negative manner. Mutations in both DICER1 and DROSHA impair tumor suppressor miRNA expression, such as let-7 family [170]. Additionally, pre-miRNAs are processed into mature miRNAs after exported via the nuclear membrane to the cytoplasm. The export of pre-miRNAs is mediated by exportin 5 and its cofactor [171]. Thus, a genetic defect in exportin-5 sequesters pre-miRNAs in the nucleus, decreases miRNA processing, and reduces miRNA-target suppression. The mutant form of exportin 5 does not have the C-terminal region that participates in forming the ternary structure complex (pre-miRNA/XPO5/Ran-GTP), thus pre-miRNAs amass in the nucleus of cancer cells [172].

3.5. The competitive endogenous RNA (ceRNA)

The interference between non-coding and coding RNA molecules characterizes a new way of gene regulation. The principal regulators of gene expression are miRNAs. They regulate mRNA expression through the direct binding on their miRNA Response Element (MRE) sites [173]. Besides, protein-coding RNA transcripts and other non-coding RNAs can attach to miRNAs through MRE sites. Therefore, they are known as miRNA sponge or ceRNA, since they compete with mRNA target for miRNA binding [174].

The ceRNA hypothesis proposed that in addition to mRNA, sequences of circular RNAs (circRNAs), long non-coding RNAs (lncRNAs), and pseudogenes contain MREs, inhibiting normal miRNA targeting activity on mRNA. Recent studies have found that ceRNAs are correlated with several diseases, including cancer [175–177]. Changes in the expression levels of ceRNA have to be large enough to reduce or overcome the miRNA repression on competing ceRNAs. This is characterized by RNA transcripts "switched" off or on at the transcriptional level in physiological or pathological conditions. A pseudogene of the PTEN tumor suppression gene is PTENP1. Its mRNA sequence, near to 3'-UTR, is highly homologous to the similar region in PTEN, and this characteristic of PTENP1 indicates that it could use as a ceRNA of PTENP gene [174]. Several studies showed the significance of the ceRNA mechanism in cancer cells [175, 178–180]. Tay et al. stated ceRNA regulation of PTEN in prostate cancer and glioblastoma cells, detecting candidates through mutually targeted MRE enrichment analysis [179]. They had observed that mRNA sharing the most miRNA binding sites that were coexpressed with PTEN would potentially bind PTEN-targeting miRNAs and relieve their repression of PTEN. Along with the variety of bioinformatics and experimental approaches used in the above-mentioned studies, these attributes of PTEN may notify the future identification of ceRNA cancer-relevant regulatory networks and their pathological dysregulation. Most notably, ceRNA function is a well-established route of participation of circular RNAs (circRNAs) in the neoplastic transformation. These covalently enclosed single-stranded RNAs have been shown to act as sponges for miRNAs, thus sequestering miRNAs and attenuating their functional roles. [181]. For instance, ciRS-7 has tens of

conserved binding sites for miR-7 [182], thus having high efficiency for sponging this miRNA. Moreover, circHIPK3 can serve as a molecular sponge for several miRNAs [181], including those being involved in the neoplastic transformation.

4. Onco-miRs and tumor-suppressor-miRNAs

Genome expression studies propose interesting different perspectives on participation of miRNAs in human neoplasms. miRNAs have been associated with different cellular functions including controlling cellular proliferation, differentiation and programing of cell death [183]. It was found that miRNAs can act as either tumor suppressor genes by targeting oncogenic mRNAs or oncomiRs, probably through several mechanisms, such as elimination of tumor suppressor proteins. For example, miR-125b exerts as a tumor suppressor effects in various solid tumors because its expression decreases the expression of LIPA, PCTP, ACCS1, HK2 GSS, IKZF4, SCD1, and TP53 [184]. On the other hand, miR-125b is an oncomiR in most of human leukemias such as AML [185], AMKL [186], CML [187] and ALL [188]. Indeed, miR-125b mostly exerts its oncogenic role by repression of hematopoietic differentiation factors (PRDM1, CBFB, IRF4, IL10RA, IL2RB) or by direct targeting the metastasis gene promoters (LIN28B, ARID3B, MMP13), metastasis inhibitors (TP53INP1, STARD13) and pro-apoptotic factors (BAK1,TP53, BMF, MAPK14, BBC3) [189–192]. Another instance of this fact is given by the miR-155 which possesses an oncogenic role in many hematological and solid malignancies, so it is considered as an oncomiR [193]. High levels of miR-155 directly targets SHIP1 and IL-6 pathway, a negative regulator of B-cell differentiation promoting the accumulation of apoptosis-resistant pre-BI cells [194]. However, despite its strong oncogenic effects, Levati et al. found that miR-155 impedes cancer proliferation and induces apoptosis process in several melanoma cell lines in which it acts as tumor suppressor, due to silencing of SKI gene [195]. Similarly, Qin et al. and Li et al. showed that miR-155 acts as tumor suppressor in ovarian and gastric cancer-initiating cells by directly targeting CLDN1 and SMAD2, respectively [195,196].

Variation of genomic miRNA within target sites may be a major source for genetic differences in cancer risk. Numerous studies have revealed that polymorphisms and mutations lead to functional loss or modification of existing miRNA target sites [193,194] and the formation of new miRNA binding sites [197]. Even within a single cancer type, the variance of a miRNA being oncogenic or tumor-suppressive is highlighted in this set of studies.

5. miRNA profiling as a new clinical tool

Since various studies proved participation of miRNAs in carcinogenesis and metastasis, miRNAs are currently being investigated to have a great role in prognostic and diagnostic methods. It was proved that a unique signature of thirteen miRNAs was correlated with disease progression in CLL [198]. Further investigation showed that expression of numerous miRNAs could accurately distinguish ALL cases with frequent translocations from other subjects [199]. Additionally, low expression of let-7a-2 and high expression of miR-155 were related with poor clinical outcome in lung cancer [200].

Numerous studies indicated that miRNAs can be biomarkers in prognosis and diagnosis [199,201]. Carme et.al. stated that the level of miR-210 expression was conversely associated with disease-free survival proposing that miR-210 might be an independent prognostic factor for early breast cancer patients [202]. Intriguingly, a recent study using microarray profiling to investigate the patterns of miRNA expression showed the association between upregulation of miR-21 and advanced clinical stage, lymph node involvement, and patient poor survival [203]. Moreover, downregulation of miR-126 and miR-335 expression was strongly associated with metastatic regression in breast cancer patients [204]. miRNAs have been found as biomarkers in biopsy specimens. In addition, more recently, various reports recommended that free circulating miRNAs are measurable in plasma or serum and the levels of tumor-associated miRNAs increased in multiple tumors such as prostate cancer [205], lung cancer [206], colorectal cancer [207], and ovarian cancer [208] and other cancers[209,210]. These results indicate that blood-based miRNAs might emerge as innovative source of biomarkers for diagnosis of different types of cancer.

6. miRNAs as drugs or therapeutic targets

Many preclinical and in vitro studies have inhibited oncomiRs or reintroduced oncosuppressive miRNAs in cancer cells, proving that these therapies are effective in inhibition of cell migration and proliferation or enhancement of cell death. This indicates that these miRNAs (oncomiRs or oncosuppressor miRNAs) could be used as drugs or therapeutic targets. The advantage of modulating miRNA expression instead of genes is their ability to target various genes and pathways simultaneously. Also, one oncosuppressive miRNA might strongly decrease the risk of resistance to therapy by targeting critical genes. Conversely, the miRNA effect on the expression of various genes may also have clinically significant side effects due to inaccurate target effects. Besides, miRNA delivery as anticancer therapies is one of the big issues, because a system might be necessary in which miRNAs should be delivered to every tumor cells, otherwise untreated cells could help tumor recurrence.

Moreover, re-expression of oncosuppressor miRNAs might be blocked the progression of cancer in vivo [211]. *In vivo* model systems have shown the efficacy of this method in suppression of cancer cells proliferation and stimulation of apoptosis without toxicity. Oncosuppressor miRNAs induction has also been shown to be used in epigenetic control. Different drugs have been used for remodeling of chromatin to inhibit methylation of DNA and deacetylation of histone, amending epigenetic alterations in cancer cells [75]. This understanding recommends that miRNAs delivery could be an essential therapeutic strategy. Recently, inhibition of miR-124 and prevention of DEN-induced HCC in animals support application of this kind of anticancer therapeutic approaches [212]. There are several systems for miRNA delivery as therapies, such as antisense oligonucleotide inhibitors of miRNAs, double-stranded oligonucleotides, anti-miRs, and miR-mimics to restore miRNA function. These innovative miRNAs therapeutic systems open the potential for a novel therapeutics class and recommend a unique cancer treatment approach via modulating the entire biological pathways.

7. Conclusion

It is evident that miRNAs participate in tumorigenesis and control the progression of human neoplasms. While many improvements have been made in the knowledge of miRNA involvement in cancer, further understanding of existing form and biological function is necessary, as many questions still need to answer. The greatest challenge for the future will be the concept of cancer-specific miRNA signature that could be used for miRNA-based cancer therapeutic and diagnostic approaches.

Conflict of interest statement

The authors declare they have no conflict of interest.

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