Review Article

From conventional therapy toward microRNA-based therapy in acute promyelocytic leukemia

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Abstract

Acute promyelocytic leukemia (APL) is a hematopoietic malignancy that is known with its special cytogenetic feature. Several studies have surveyed expression signature of microRNAs (miRNAs) in APL patients, especially patients who are treated with conventional therapy of this disease. Using miRNAs as diagnostic or prognostic biomarkers in various cancers has been widely studied. Currently, most studies are focusing on exploiting miRNAs as therapeutic tools, and promising progress has been achieved in this field. Recently, studies in the field of miRNA-based therapy in APL have been started.

Key Words: Acute promyelocytic leukemia, cancer therapy, microRNAbased therapy

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INTRODUCTION

According to the French–American–British classification, acute promyelocytic leukemia (APL) is an M3 subtype of acute myeloblastic leukemia (AML) and accounts for 10–15% all types of AML. Now, however, in the World Health Organization classification system, APL is classified as APL with t(15;17)(q22;q12); promyelocytic leukemia-retinoic acid receptor α (PML-RARα). In this malignancy, arrest of leukocyte differentiation takes place on promyelocyte stage.[1,2] Because of the high mortality rate from this disease, APL has ever been considered the most deadly type of AML.[3] Since the identification of this cancer, there have been many attempts to treat it which consists mainly of chemotherapy, all-trans retinoic acid (ATRA) and recently arsenic trioxide (As_2O_3 or ATO). These are used alone or in combination with each other. Despite significant progress in this context, in some cases, these strategies for treatment are not effective. With the advent of microRNAs (miRNAs), hopes for treatment of many diseases, especially cancer, increased.[4] They is a class of evolutionary conserved single-stranded noncoding RNAs with approximately 19–25 nucleotides which have a key function in posttranscriptional gene expression regulation in processes such as proliferation, development, differentiation, and apoptosis.[5] miRNAs modulate a major part of the human genome and increasing evidence suggests that expression of them are deregulated in diseases, especially in cancers.[6] The aim of this review article is to compare the role of miRNAs as therapeutic tools for cancers such as APL with conventional therapy of this disease.

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CHARACTERISTIC OF ACUTE PROMYELOCYTIC LEUKEMIA

This rare but deadly leukemia involves some specific chromosomal rearrangements that in almost most cases (>98%) are a balanced reciprocal translocation between chromosomes 15 and 17, which leads to the creation of fusion protein between the PML gene and the RARα gene.[7,8] Generated fusion protein has properties of an incorporation that facilitate a block in myeloid differentiation by suppressing the transcription of retinoid acid (RA) responsive genes.[9] This constitutive suppression is conducted by recruiting abnormal transcription factors and epigenetic enzymes such as histone deacetylases and DNA methyltransferase on retinoic acid target gene promoters.[10,11]

CONVENTIONAL ACUTE PROMYELOCYTIC LEUKEMIA THERAPIES

Initially, treatment of APL was performed by chemotherapy with an anthracycline (daunorubicin, idarubicin, or others) and cytarabine arabinoside as frontline treatment similar to all other subtypes of AML.[12] This approach achieved complete remission (CR) in 75–80% of patients[13] but associated with a high early death rate for some reasons such as deterioration of preexisting disseminated intravascular coagulation because of the release of azure granules in the malignant cells. Despite a high sensitivity to anthracycline, merely about 45% are cured only through standard chemotherapy.[14]

In recent decades, the introduction of ATRA has revolutionized APL therapy. The current standard treatment for APL is based on a combination of ATRA with anthracycline-based chemotherapy.[15] After starting induction therapy with ATRA, one problem that may occur in some patients is symptoms of differentiation syndrome (DS). The combination of ATRA and chemotherapy, therefore, has a major challenge because of death induction due to infection and DS.[16]

In 1971, researchers at the Harbin Medical University in China found that As_2O_3 or ATO, a traditional Chinese medicine, has significant impact on the treatment of APL.[17]

Unlike ATRA that targets RARα moiety of fusion protein, ATO targets the PML moiety, and both of them degrade PML/RARα.[18] In animal models, synergistic effect was revealed for clearing APL cells.[19] The ATO alone or combination of ATO and ATRA is more effective in inducing CR in newly diagnosed and relapsed patients with low and intermediate risk. In high-risk cases of APL, ATRA/chemotherapy remains the preferred approach.[20] Two major obstacles for using of ATO treatment is that it is much more expensive than chemotherapy and partly associated with toxicity. In a study, it was revealed that using ATRA in combination with the ATO has less hematologic toxicity and less infections than ATRA plus chemotherapy, although coupled with more hepatic toxicity.[16]

BIOGENESIS AND MECHANISM OF MICRORNA

miRNA biogenesis starts through transcription of either particular genes or introns by RNA polymerase II.[21-24] The generated transcript is a long primary miRNA (pri-miR) which folds into a hairpin structure and similar to other mRNAs is capped with 7-methyl-guanosine on the 5′ end and with a polyadenylation tail on the 3′ end. Then an enzyme called Drosha with its cofactor, DiGeorge syndrome critical region 8, processes pri-miR to produce ~70 nucleotide precursor miR (pre-miR).[25]

Complex of exportin 5 and Ran-GTP recognizes this pre-miR and transport it into the cytoplasm. In the cytoplasm, a double-stranded RNA-specific RNaseIII endonuclease (Dicer) cleaves pre-miR's terminal loop by its dsRNA binding partner, resulting in a mature miRNA [Figure 1].

Mature miRNA is then unwound and incorporated into the RNA-induced silencing complex (RISC). miRNAs via the RISC bind to 3′-untranslated region of the target mRNA(s) and acts as endogenous suppressors of gene expression.[26] If the miRNA binds incompletely to the target mRNA, represses translation of mRNA, whereas if the binding is almost complete, the miRNA induces degradation of the mRNA.[27] Seed region, nucleotides 3-8 from the 5′ end of the mature miRNA, is the crucial binding location for translational repression.[28] Some miRNAs might indirectly regulate gene expression through the targeting of transcription factors and other miRNAs directly target 5′ region, ribonucleoproteins, and promoters.[29] Some miRNAs activate, rather than inhibit, gene expression of their targets by binding directly to the 5′ UTR.[30]

THE FUNCTIONS OF MICRORNAS IN CANCER

In the last decades, researchers have found that the expression patterns of miRNAs are dysregulated in various cancers.[31,32] Increasing evidence show that miRNAs can act as a tumor suppressor or an oncogene. miRNAs that act like tumor suppressor genes include a group of these noncoding RNA whose

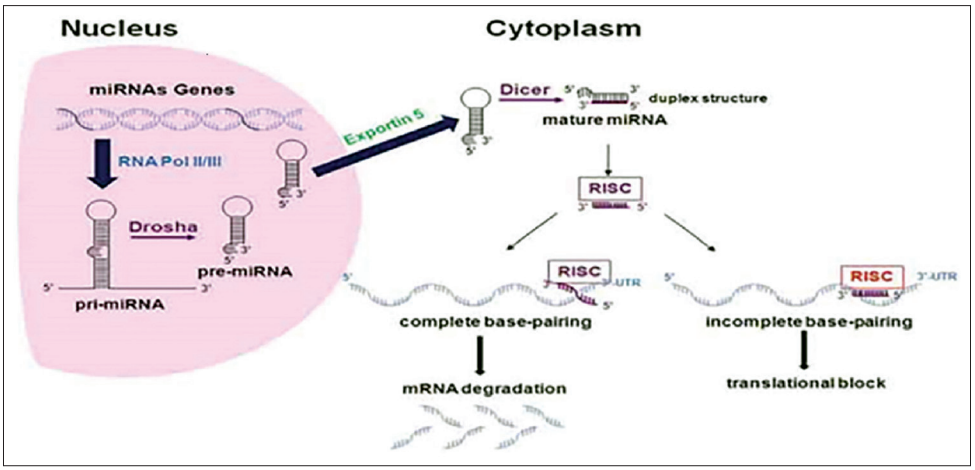

Figure 1: Schematic representation of biogenesis and mechanism of microRNA[27]

loss of function promotes cancer development.[33] This category of miRNAs act similar to protein-coding tumor suppressor genes. They are involved in many cancers [Table 1].

Oncogenic miRNAs (oncomiRs) are a category of miRNAs that upregulation of them lead to an acceleration of tumor formation and development.[43] The two hallmarks of cancer that are mostly affected by oncomiRs are metastasis and proliferation of tumor cells.[44] OncomiRs through targeting of mRNAs which are encoded by tumor suppressor genes can affect tumorigenesis.[45] Recently, many oncomiRs have been known to be dysregulated in various tumors. Some examples of them are summarized in Table 2.

THE ROLE OF MICRORNAS IN NORMAL HEMATOPOIESIS

The important role of miRNAs in hematopoiesis was found by identifying three murine hematopoietic tissues-specific expressed miRNAs, miR-181a, miR-142s, and miR-223. miR-142s expression was found to be limited to B-lineage and myeloid lineages, and miR-223 was found to be expressed in myeloid lineages. Considerably, deregulation of expression of miR-223 or miR-142 leads to 30–50% increase of T-lineage cells, but do not affect the numbers of B-lineage or myeloid cells. It was revealed that miR-181a preferentially expresses in the B-lineage and ectopic expression of this miRNA resulted in a doubling of B-lineage cells.[55] Altogether, these results show that miRNAs might have an important role in the differentiation of hematopoietic cells.

A very strong relation between the miRNAs expression profile and differentiation stage of murine hematopoietic cell populations was revealed by comparison of cell populations at different stages of differentiation. However, the correlation between precursor cells and their corresponding mature cell populations were much less.[56] This verifies the importance role of miRNAs in the differentiation and keeping of hematopoietic maturation stages.

Some studies have revealed the expression of pri-miR-155 in lymphoid tissues and T and B cells.[57,58] In lymphoid tissues, confirmation of expression of the B-cell integration cluster (BIC) locus-derived miR-155

Table 1: Examples of tumor suppressor microRNAs reported to be downregulated

miRNAs	Cancer type	Reference
miR-551a	Gastric cancer	[34]
miR-494	Lung cancer	[35]
miR-495	Acute myeloid leukemia, gastric cancer	[34]
miR-155	Breast cancer	[36]
miR-375	Breast cancer	[37]
miR-181a/b	Acute myeloid leukemia	[38]
miR-150	Acute myeloid leukemia	[39]
miR-29b	Acute myeloid leukemia	[40]
miR-126	Breast, lung, and colon cancers	[41]
miR-34b/c	Lung cancer	[42]

miRNAs: MicroRNAs

Table 2: Examples of oncogenic microRNAs reported to be upregulated

miRNAs	Cancer type	Reference
miR-9	Acute myeloid leukemia	[46]
miR-421	Gastric cancer	[47]
miR-17-92	Acute myeloid leukemia	[48]
miR-196a	Gastric cancer	[49]
miR-21	Breast cancer	[50]
miR-181a/b	Breast, liver, and colon cancers	[51]
miR-27a	Nonsmall cell lung cancer	[52]
miR-126	Acute myeloid leukemia	[53]
miR-30a/c	Nonsmall cell lung cancer	[54]

miRNAs: MicroRNAs

in tonsil and lymph node was confirmed by Northern blotting.[59] By applying anti-CD3 in combination with anti-CD28, stimulation of CD4+ T-cells result in a sharp rise in expression of BIC.[60] The results propose a correlation between induction of high BIC/miR-155 and activation of T and B-cells.

miR-221 and miR-222 were found to be downregulated in erythropoietic cells at different stages of erythrocyte differentiation and maturation. Both miRNAs are identical at the first eight nucleotides of the 5′ sites (seed region) that indicate overlapping in their target genes. Through prediction studies, it was revealed that KIT receptor is a target for both miR-221 and miR-222. C-KIT play an important role in the proliferation control of primitive hematopoietic and erythropoietic cells, and it was revealed that following erythrocyte differentiation, the expression of miR-221/miR-222 and KIT are inversely correlated.[61]

In two studies, researchers exploited generation of conditional DICER-1 knockout alleles to clarify the general role of miRNAs in murine T-cell differentiation.[62,63] Both studies revealed decreased viability of T-cells.

MICRORNAS IN ACUTE PROMYELOCYTIC LEUKEMIA

By studying an APL model system, linking of miR-223 expression to the retinoic acid signaling pathway and CCAAT/enhancer binding protein-α in normal human granulopoiesis was obtained.[64] miRNAs expression profiling of AML patients has shown that by analyzing miRNA signatures, we can distinguish between cytogenetic subtypes of AML.[53,65,66] Dixon-McIver *et al*. identified a special expression profile of miRNAs in APL patients. It included upregulation of miR-127, miR-154 *, miR-299, miR-323, miR-368, and miR-370 which their genes located in the 14q32 and nine other miRNAs were downregulated.[65] The two other studies also determined two different signatures of a gene cluster.[53,66]

Some roles of miRNAs in APL were identified by studies that surveyed the effect of conventional treatment on expression of miRNAs. By using RA treatment, it was revealed that RA without affecting the expression of miR-142 or miR-181a, exclusively increase the expression of miR-223.[67] While ectopic expression of miR-223 increases differentiation of NB4 cells, knock down the miR-223 inhibits the effect of RA on the differentiation of cells.[64] De Marchis *et al*. showed that miR-342 mediates ATRA effect on APL differentiation in combination with PU.1 and interferon regulatory factor proteins.[68] In another study, it was revealed that during ATRA therapy in APL patients and APL cell lines, some miRNAs are differentially expressed.[69] Zhong *et al*. revealed that during ATRA induction, miR-146a modulate proliferation of APL cells through transforming growth factor-beta 1/Smad signal transduction pathway which inactivation of it is related to human leukemia.[70] One study showed that ATO can modulate 88 cancer-related miRNAs.[71] Construction of a dysregulated miRNA network was performed in a study that examined the effect of ATO on apoptosis of APL cells.[72]

MICRORNA-BASED CANCER THERAPY

miRNA-based therapy mainly depends on nucleic acid-based strategies. The aim of these strategies is to restore the normal function of miRNAs. Targeting overexpressed oncomiRs is conducted mainly by two methods: Antisense oligonucleotides (antagomiRs) and miRNA sponges.

Antisense molecules that are chemically modified and have a bridge between the 2′-O and 4′-C at each nucleotide are called locked nucleic acid (LNA) oligonucleotides and are used for synthesizing anti-miRNA nucleic acids.[73,74]

miRNA antagonists (antagomiRs) contain 3′-conjugated cholesterol residues, 2′-O-methylation of ribose residues, and substitutionary of phosphodiester bonds through phosphorothioate linkages.[75] AntagomiRs affect cancer-related pathway through binding and inhibiting oncomiRs. In some studies, the effectiveness of this method has been surveyed.[76,77]

miRNA sponges are produced from transgenes within cells and have complementary binding sites to seed sequences of target miRNAs. This advantage gives them the ability to inhibit a family of miRNAs.[78] It has been revealed that using miR-9 sponges, the activity of this miRNA is reduced to 50%.[79]

miRNA replacement therapy or miRNA mimics method mostly has conducted in animal models. In this method, malfunctioning tsmiRs are replaced.[80] In the field of cancer treatment, exploiting MRX34 is the first example of miRNA-based cancer therapy. MRX34 is a synthetic miR-34a mimic that is transferred by liposomal nanoparticles.[81] miR-34a is a tsmiR downstream of p53 and using replacement strategy, it counteracts chemoresistance and self-renewal of cancer cells.[82] In a study, introduction of lentiviral Let-7 miRNA into self-renewing breast cancer cells lead to an increase in Let-7 level.[83] In other studies, it was shown that we can restore downregulated tsmiRs

miR-205, miR-126, miR-335, and miR-451 by using miRNA replacement therapy.[84,85]

Few studies have been conducted on the use of miRNA therapy in APL. Inhibition of miR-92a by LNA in HL-60 (human APL cell line) induced apoptosis and inhibited cell proliferation through the expression of p63 and following the recovery of cellular pathways which are modulated by p63 protein.[86-88]

CONCLUSION

In the past decade with the advent of the term "personalized medicine," targeted-therapy of diseases, in particular, cancer has been taken into consideration. As well as in hematological malignancies such as APL attempts have been made. The emersion of ATRA made changes in this area of therapy and, in fact, ATRA is the first example of targeted therapy in cancers. However, despite the efforts that have been made to improve the quality of APL treatment such as ATO-based drugs, still we need methods that are more efficient. miRNA-based therapy is a new and attractive method in this field. As previously mentioned, several *in vitro* studies have been conducted. This method has its limitation which should be considered, such as the paucity of preclinical and clinical studies. Our knowledge about miRNA is still in its infancy, methods that are used for delivery and entry into cells have problems and "off-target effect" of this technique because of any miRNA has many targets and its expression is regulated by several genes. Therefore, prior to use in clinical, many of the problems related to it must be resolved. Undoubtedly, with establishing miRNA-based therapy in the clinic as an effective therapeutic tool, we can prevent many of the side effects of chemical drugs, especially those which are used in chemotherapy.

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Conflicts of interest
There are no conflicts of interest.

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