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miRNAs in Acute Lymphoblastic Leukemia: Diagnosis, Prognosis and Target Therapeutic

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Abstract

Acute lymphoblastic leukemia (ALL) is more frequent in children than in adults. The ALL is a hematological neoplasia, which is characterized by the hyperproliferation of lymphoid precursors in bone marrow. MicroRNAs (miRNAs) are a class of noncoding RNAs that regulate mRNA expression at posttranscriptional level. miRNAs regulate different biological processes such as development, proliferation, apoptosis, hematopoiesis, drug resistance, and tumorigenesis. It has also been observed that the expression of miRNAs can be used to the classification of the different subtypes of ALL. Likewise, miRNAs can also be used to determine the prognostic value and may represent potential therapeutic target molecules in the treatment of ALL.

Keywords: miRNAs, acute lymphoblastic leukemia, diagnosis, prognosis, therapy, biomarkers

1. Introduction

The hematopoiesis is primarily regulated at the transcriptional level by transcription factors that act as master regulators of genes expression. However, the transcriptional process alone does not appear to control all aspects of cellular functioning (cell fate, lineage, etc.), suggesting the participation of other mechanisms. The miRNAs constitute another critical way of hematopoietic regulation. The B- and T-lymphocytes develop from progenitor cells that occur in different organs; B-cell lymphopoiesis is completed in the bone marrow, whereas T-cell lymphopoiesis occurs in the thymus. However, their development and activation are controlled by signaling pathways, which are also regulated by the microRNAs (miRNAs) [1]. miRNA expression profile during the normal and malignant hematopoiesis suggests that miRNAs are regulators of hematopoiesis implicated in regulating and maintenance of the "stemness" of the early progenitors, various stages of cell differentiation, and malignance [2].

Nowadays, there is evidence that miRNAs do not just regulate hematopoietic differentiation and proliferation but also their activity. Deregulation of the expression of miRNAs has been observed in leukemias, and mechanistic studies reveal a role for miRNAs in the pathogenesis of this disorder [3].

Leukemia is a clonal disorder in which the normal hematopoiesis is replaced by a malignant clonal expansion of immature hematopoietic cells (blasts) in the bone marrow or peripheral blood [4]. The first approach between miRNAs and leukemia was carried out by Calin et al. [5]. The author showed that the 13q14 deletion in B-cell chronic lymphocytic leukemias (B-CLLs) causes the loss of the precursor gene of miR-16-1 and miR-15a; therefore, the loss of these miRNAs is observed in approximately 70% of the CLLs [5]. Interestingly, it has been reported that at fragile sites, minimal regions of amplification (minimal amplicons), or common break-point regions fragile sites, minimal regions of loss of heterozygosity, and genomic regions related with cancer code for approximately 50% of the miRNAs, hence the aberrant expression of different miRNAs in cancer [6].

The participation of miRNAs in different biological and cellular processes under pathological and normal conditions makes them good candidates in the investigation of functional markers for differential diagnosis, prognosis, and development of new therapeutic regimens, through the investigation of their molecular targets. In this chapter, the role of miRNAs expression profiles in ALL that could be used for classification of the disease establishing specific diagnoses and prognostic values is summarized. Likewise, the relation between the miRNA dysregulation and ALL may be a potential therapeutic target.

2. MiRNA biogenesis

The miRNA genes are transcribed by RNA polymerase II (Pol II) in the nucleus, and the primary miRNAs transcripts (pri-miRNAs) contain cap structures as well as poly(A) tails [7, 8]. The pri-miRNA transcript is processed by the microprocessor complex (Drosha/DGCR8), which crops the pri-miRNAs, producing a pre-miRNA
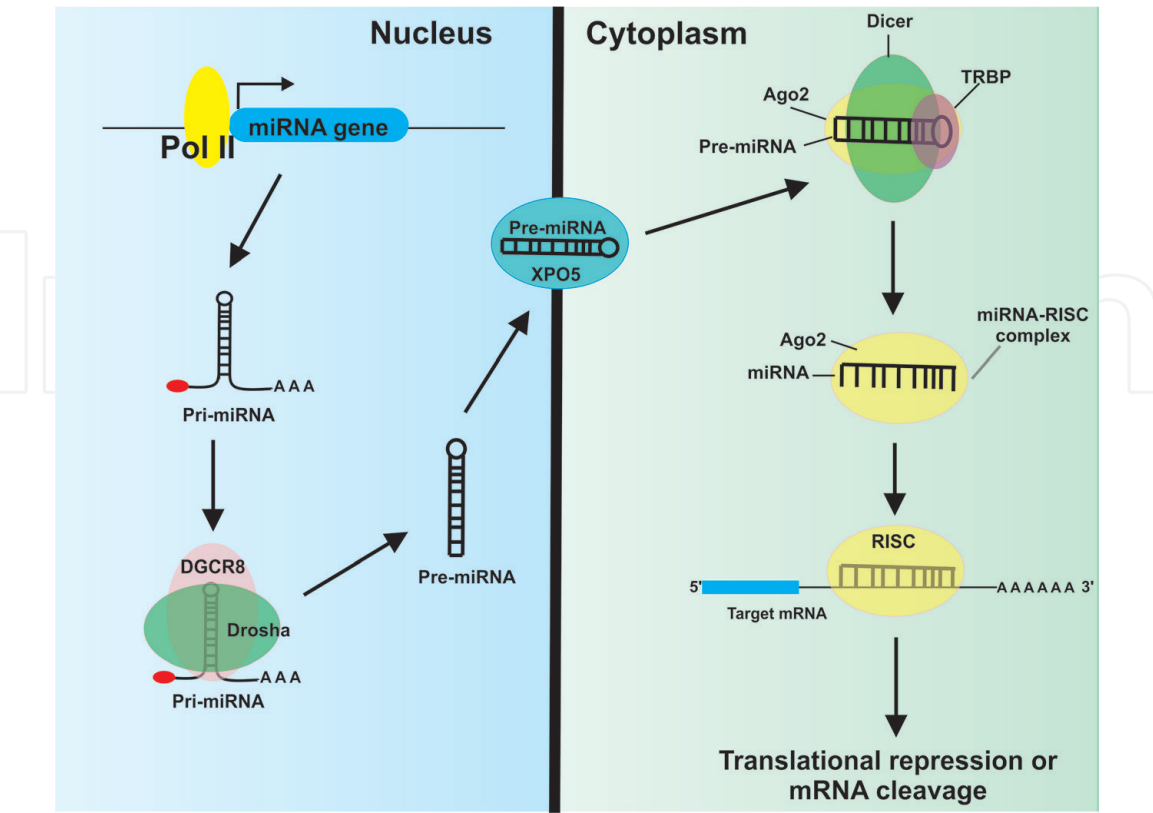

Figure 1.
miRNA biogenesis.

(transcript of about 70 kb) [9–11]. The exportin 5 (XPO5) mediates the export of the pre-miRNAs from the nucleus to the cytoplasm [12–14]. In the cytosol, the pre-miRNA is recognized by Dicer enzyme (RNAse type III), producing a mature **miRNA duplexes** (miRNA:miRNA*) about 22 nucleotides [10]. The miRNA duplex binds to the RNA-induced silencing complex (RISC) [which is composed by of the transactivation-responsive RNA-binding protein (TRBP) and Argonaute2 (Ago2)] [8, 15]. The mature strand is retained by the Ago2 protein in the RISC complex, who directs the mature mRNA to its mRNA target for posttranscriptional gene silencing, while the complementary strand is degraded [16, 17] (**Figure 1**).

3. Functions of the miRNAs in lymphopoiesis

Lymphopoiesis is a process by which the hematopoietic stem cells (HSCs) differentiate into lymphoid progenitors and finally into B- or T-lymphocytes [18]. In the process of differentiation, the miRNAs play an important role. miR-29a and miR-196b are highly expressed by HSCs, and their downregulation is associated with differentiation into lymphoid progenitors [19, 20]. It has been reported that miR-17, miR-24, miR-155, miR-128, and miR-181 act to prevent the differentiation of early-stage progenitors [21].

miRNA-150 is expressed in both mature B- and T-cells. The lymphoid progenitors express the miRNA-150 to give rise to the mature B-cells and assist in the transition from progenitor B-cell (pro-B) to the precursor B-cell (pre-B) stage [18]. And premature expression of miRNA-150 results in blocked transition from the pro-B-cell stage to the pre-B-cell stage [22, 23].

B-cell differentiation is regulated by the miR-155, and it has been observed that miR-155 levels are upregulated rapidly in both activated mature T- and B-cells [24]. Also, miRNA-155 regulates the differentiation of T-cells into Th type 1 cells [24, 25].

miR-181 is specifically expressed in hematopoietic cell, and its expression is dynamically regulated during early hematopoiesis and lineage commitment. miR-181 expression is high in the early B-cell differentiation stage and progressively decreases subsequently, and its ectopic expression in hematopoietic stem/progenitor cells led to an increased fraction of B-lineage cells in both tissue culture differentiation assays and adult mice [26]. Additionally, miR-181 also plays an important role in T-cell development [27].

The miRNA-15 family is an element required to promote the switch from pre-B-cell proliferation to a more differentiated stage. [28]. So, pre-B-cells lacking miRNA-15 family functions exhibit prolonged proliferation because of aberrant expression of the target genes cyclin E1 and D3, and they additionally fail to trigger the transcriptional reprogramming normal to their differentiation, resulting in a developmental block at the pre-B-cell stage [28].

Six miRNAs, miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a-1 are part of the miR-17-92 cluster; these small molecules are important for mature B-cell development. Absence of the cluster leads to the development of disorders in the maturation from pro-B to pre-B stage [29]. Ventura et al. using miR-17-92-deficient mice found that B-cell development is inhibited at the pro-B to pre-B stage differentiation [30]. The above shows that if the miR-17-92 family miRNAs control the pro- to pre-B transition during B-cell development [31]. Likewise, it has been showed that in helper T cells, the miR-17–92a cluster is critical for the differentiation from Th1 cells [32].

miR-29b is increased in Th1 cells, and the levels from this miRNA decrease significantly upon T cell activation. So, the miR-29 expression can serve as a regulator

of Th1 differentiation [33]. Expression of miR-21 promotes Th2 differentiation in nonpolarized T cells [34]. miR-126 is another miRNA that also regulates the differentiation of the Th2 cells [35].

4. miRNA expression and its role in the differential diagnosis of acute lymphoblastic leukemia subtypes

Acute lymphoblastic leukemia (ALL) is characterized by clonal proliferation of early B- and T-lymphocyte progenitors that result in the accumulation of lymphoblasts in the bone marrow and various extramedullary sites. ALL is also the hematology neoplasia most commonly observed in the pediatric population, while it is relatively **less common than AML** in adults [36]. Around 75% of childhood ALL cases contain at least one alteration chromosomic, have lymphoid maturation arrest in distinct stages, and involve B- or T-lineages to leaving different immunophenotypes with different miRNA signatures [37].

microRNAs participate in different physiological and cellular processes, such as development and tissue differentiation, cell identity, cell cycle progression, and programmed cell death [38]. Nowadays, it is known that the distinct stages of lymphopoiesis and the direction of lymphoid precursor maturation are influenced by miRNA expression differentially. However, an aberrant expression of miRNAs is related with malignant lymphopoiesis, characteristic that can be utilized as signature to diagnosis and classification diagnosis of acute lymphoblastic leukemia [18]. Interestingly, miRNA groups that can clearly differentiate ALL of its normal counterpart, B-ALL versus T-ALL and ALL subtypes with specific genetic abnormalities have been reported. De Oliveira and collaborators reported miRNA-128a and miRNA-181b overexpressed and miRNA-100, miRNA-196b, and let-7e with lower level when compared the miRNAs expression in normal pediatric bone morrow (BM) samples and BM samples of pediatric ALL. The authors point out miR-196b as a miRNA highly expressed in T-ALL, while miR-100 was related with the presence of t(12;21) [39].

A study in Brazilian children with T- or B-cell acute lymphoblastic leukemia (T-ALL or B-ALL) evaluated a bone marrow miRNAs profile that may be used for distinguishing childhood lymphoblastic leukemia subtypes [40]. The authors mention that miR-708-5p, miR-497-5p, miR-151a-5p, miR-151b, miR-371b-5p, miR-455-5p, miR-195-5p, miR-1266-5p, miR-574-5p, miR-425-5p downregulated and miR-450b-5p, miR-450a-5p, miR-542-5p, miR-424-5p, miR-629-5p, miR-29c-5p upregulated in childhood T-ALL may be used for distinguishing childhood T- and B-ALL subtypes. However, a machine learning analysis showed that miR-29c-5p, which is involved in calcium signaling, is critical for B-cell lymphocyte fate. So, it is the best discriminator between childhood T- and B-ALL [40].

In a series of adult ALL cases, the expression profile of 470 miRNAs was measured by microarray analysis; 3 miRNAs (miR-148, miR-151, and miR-424) were identified as discriminative of T-lineage versus B-lineage ALL; and miR-151 dramatically downmodulated an miR-148a and miR-424 with higher expression in patients with T-ALL [41]. Furthermore, in the B-lineage ALL cases with special molecular lesions, those with BCR/ABL, E2A/PBX1, MLL/AF4 rearrangements and cases lacking known genetic abnormalities can be differentiated by a set of six miRNA, which was highlighted by one-way analysis of variance [41]. These miRNAs were preferentially expressed in each chromosomal rearrangement; miR-425-5p, miR-191, and miR-128 were expressed in the E2A/PBX1-positive case, miR-629 was highly expressed in cases harboring MLL/AF4 rearrangement, while high levels of miR-146b and miR-126 were observed in the BCR/ABL-positive cases [41]. Other study in pediatric ALL showed

ALL subtype	Upregulated expression	Downregulated expression	References
Children			
T-ALL	miR-450b-5p, miR-450a-5p, miR-542-5p, miR-424-5p, miR-629-5p, miR-29c-5p	miR-708-5p, miR-497-5p, miR-151a-5p, miR-151b, miR-371b-5p, miR-455-5p, miR-195-5p, miR-1266-5p, miR-574-5p, miR-425-5p	[39]
MLL-rearranged, T-ALL	miR-196b		[41]
TEL-AML1 BCR-ABL, E2A-PBX1, hyperdiploid, and B-other	miRNA-708		
Adults			
T-ALL	miR-148a, miR-424	miR-151	[40]
E2A/PBX1-positive B-ALL	miR-425-5p, miR-191, miR-128		
MLL/AF4-positive B-ALL	miR-629		
BCR/ABL-positive B-ALL	miR-146b, miR-126		

Table 1.
Expression of miRNAs in children and adults to differentiate acute lymphoblastic leukemia subtypes.

in seven major subtypes of pediatric ALL, which included: T-cell, MLL-rearranged, TEL-AML1-positive, E2A-PBX1-positive, hyperdiploid ALL, BCR-ABL-positive, and B-other ALLs, the differential miRNA expression. miRNA-708 was highly expressed in TEL-AML1, BCR-ABL, E2A-PBX1, hyperdiploid, and B-other cases than in the MLL-rearranged and T-ALL cases. On the other hand, the expression of miR-196b was higher in MLL-rearranged and T-ALL cases as compared with the expression level in the precursor B-ALL cases [42]. This information suggests that upregulated expression of miR-424 and downregulated expression of miR-151 might be good diagnostic markers to differentiate T-ALL regardless of age (**Table 1**).

Malik and collaborators propose a novel miR-2909-KLF4 molecular axis to differentiate the pathogeneses of pediatric B- and T-cell ALLs that may represent a new diagnostic marker, through alterations in miRNA expression patterns and their respective targets. The authors demonstrate the ability of miR-2909 to repress KLF4 expression in pediatric B-ALL, but not T-ALL [43]. Another interesting work shows that miR-19b, miR-20a, miR-26a, miR-92, and miR-223 have cooperative effects on tumor suppressor genes implicated in the pathogenesis of T-ALL, including *IKAROS*, *PTEN*, *BIM, PHF6, NF1,* and *FBXW7*. Interestingly, these miRNAs are capable of promoting T-ALL development in a mouse model [44].

5. MicroRNAs as prognostic markers in ALL

MiRNAs are suggested as promising biomarkers not only in the diagnosis but also in the prognosis of ALL patients. Since they have been promising in identifying subgroups of patients with different clinical outcomes [45]. It has been observed that ectopic expression of miRNAs leads to the development of leukemia, such is the case of miR-125b, which has been reported in mice transplanted with fetal liver

cells ectopically expressing miR-125b that showed an increase in white blood cell count, in particular in neutrophils and monocytes, associated with a macrocytic anemia. These mice developed B-cell acute lymphoblastic leukemia, T-cell acute lymphoblastic leukemia, or a myeloproliferative neoplasm, suggesting an important role for miR-125b in early hematopoiesis [46].

Patients group with high miR-21 expression was significantly associated with those aged <2 and > 10 years, lower platelets count, more incidence of central nervous system (CNS) infiltration, and poorer treatment outcome also; patients with high miR-21 showed a significantly poorer disease-free survival (DFS) and overall survival (OS) compared with those with low miR-21 expression group [47]. Also, miR-92a expression is significantly higher in ALL compared with peripheral blood mononuclear cells (PBMNCs) from healthy volunteers. Likewise, the expression levels of miR-99a, miR-100, and miR-128b correlated high-risk prognostic factors, including white blood cell (WBC) count, ALL subclassification (T-cell and B-cell ALL), the MLL-rearranged gene, and the BCR-ABL fusion gene, suggesting possible relation of miR-99a, miR-100, and miR-218b with prognosis [48, 49]. It has also been reported that mir-125b-2 is highly expressed in childhood ETV6/RUNX1 (TEL/AML1) leukemias and confers survival advantage to growth inhibitory signals independent of p53 [50].

More specifically, miR-9, miR-24, and miR-92a expression was significantly increased in a subset of ALL cells, and ALL patients with overexpressed miR-24 and miR-92a had poor prognoses [51–53]. Wang et al. (2010) observed that miR-146a, miR-181a/c, and miR-221 were significantly associated with overall survival of the ALL patients. Expression level of miR-146a and miR-181a/c was associated with a poor outcome (i.e., poor prognosis/short-term survival), whereas that of miR-221 was associated with a good outcome (i.e., good prognosis/long-term survival) [54], while that of miR-423-5p is associated with a poorer survival in patients with ALL [55]. Otherwise, the reduced expression of miR-155, miR-181b, miR-182, miR-143, miR-210, and miR-335 is associated with poor outcome of pediatric ALL [56–60]. Also, the expression of miRNAs miR-18a, miR-532, miR-218, miR-625, miR-193a, miR-638, miR-550, and miR-633 is associated with early relapse in childhood ALL, suggesting possible relation of these miRNAs with prognosis [61].

The high miR-16 expression is associated with hyperleukocytosis and poor cytogenetic groups. In B-cell ALL patients, the DFS was significantly shorter in patients with high miR-16 levels. While in T-cell ALL patients, for both DFS and overall survival, a significant trend was found with a survival shortening from the lowest to the highest miR-16 levels [62, 63]. Likewise, it was reported that the expression of miR-16 was upregulated in cases of T lymphoblastic lymphoma/leukemia (T-LBL/ALL), and the high expression group of miR-16 was significantly correlated with longer over survival [64].

For instance, Gimenes-Teixeira et al. reported that T-ALL patients with high miR-221 expression had significantly lower 5-year overall survival (OS) rates compared with those with low miR-221 expression [65]. Oliveira et al. observed that lower levels of miR-29a were significantly associated with higher blast counts in the bone marrow and with increased disease-free survival in T-ALL patients [66].

6. miRNAs in response to commonly used chemotherapy agents in pediatric acute lymphoblastic leukemia

Despite the great effort of current treatment strategies, drug resistance still remains a major cause of chemotherapy failure and relapse in pediatric patients.

miRNAs have not only become tools for classifying subtypes of ALL and in support of the prognosis of this disease, but also studies have reported the classification of patients sensitive or resistant to drugs based on the expression of miRNAs.

Glucocorticoids (GCs) regulate proliferation, differentiation, metabolism, and cell survival in many tissues. In lymphocytes, they affect cell cycle progression, influence immunoglobulin and lymphokine production, and induce apoptosis in immature lymphoblasts [67]. Actually, these drugs are used clinically in the treatment of childhood acute lymphoblastic leukemia (ALL) and other lymphoid malignancies. In the group of glucocorticoids that is administered to patients with ALL is the prednisone; unfortunately, a proportion of patients are insensitive to this drug. A study in 49 ALL patients showed that miR-18a, miR-532, miR-218, miR-625, miR-193a, miR-638, miR-550, and miR-633 could distinguish prednisone-sensitive patients from prednisone-insensitive patients [68]. In contrast, other authors in a group of 81 children with newly diagnosed ALL, no discriminative microRNAs were found for prednisolone response [69].

It is well known that the presence of translocations in ALL is a frequent and prognostic influence event. In leukemia, MLL rearrangements are a common genetic alteration; MLL-AF4 acute lymphocytic leukemia (ALL), resulting from a balanced translocation between *MLL* and *AF4,* occurs in approximately 50% of ALL cases in infants, 2% in children, and 5–6% in adults. The poor prognosis of MLL-AF4 ALL to glucocorticoid-induced apoptosis is associated with its resistance to this drug [70]. miR-128b and miR-221 are commonly downregulated in MLL-rearranged ALL compared with other types of ALL; also these miRNAs downregulate mRNAs encoding CDKN1B, MLL, AF4, and both MLL-AF4 and AF4-MLL fusion genes that are thought to contribute to leukemia development [71]. Interestingly, the restoration of miRNA-128b downregulates target genes including *MLL*, *AF4*, and both *MLL-AF4* and *AF4-MLL* fusion oncogenes, and the restoration of miRNA-221 downregulates CDKN1B cooperatively. Thus, the sensitivity of MLL-AF4 ALL cells to GCs is strengthened [71]. Study developed by Kotani et al. supports the idea that restoration of miRNA-128b improves the sensitivity of MLL-AF4 ALL cells to GCs. This author mentioned that one novel mutation of miRNA-128b significantly reduced its processing, and the resultant downregulation of mature miRNA-128b gave rise to GCs resistance due to the failure to downregulate the fusion oncogenes [72]. This suggests that miRNA-128b and miRNA-221 could be GC (dexamethasone) sensitizers potential.

Other microRNAs related with drug resistance in pediatric acute lymphoblastic leukemia are miR-454, which present a low expression in L-asparaginase-resistant cases, whereas miR-125b, miR-99a, and miR-100 show an upregulation of their expression in patients resistant to vincristine and daunorubicin [69].

7. miRNAs as therapeutic targets in acute lymphoblastic leukemia

Nowadays, advances in our understanding of the molecular carcinogenesis of the human cancers and the extensive research on generate and implement new combined and targeted therapies, and have allowed to know specific molecular therapeutic targets. However, there is still a continuous need for development of new therapeutic tools for applicability.

RNA molecules actually are the therapeutic targets promising in the molecular oncology. The ability of miRNAs to regulate important cellular processes, by concurrently regulating multiple targets, their inherent role in carcinogenesis as oncogenes or tumor suppressor genes, and the aberrant dysregulation of their

expression levels in cancer, can represent a viable therapeutic strategy and a powerful intervention tool in **leukemia** [73]. For example, in leukemia cells isolated from individuals with BCR/ABL, TKI-resistant Philadelphia-chromosome-positive acute lymphoblastic leukemia (Ph + ALL) was observed an increase in levels of DNMT3A in association with downregulation of miR-217; these observations are clinically relevant; and inhibition of DNMT3A by forced expression of miRNA-217 may benefit in preventing drug resistance to TKI treatment in Philadelphia-chromosome-positive ALL patients [74]. Another therapeutic strategy for BCR-ABL-positive ALL is miRNA-203, which has as direct target to BCR-ABL1 and ABL1, proteins with activity tyrosine kinase. This miRNA is silenced by genetic and epigenetic mechanisms in hematopoietic malignancies expressing either ABL1 or BCR-ABL1. However, the restoration of the miRNA-203 expression reduces ABL1 and BCR-ABL1 levels and inhibits cell proliferation [75]. miRNA-143 was identified as a regulator of MLL-AF4 expression and is epigenetically repressed by promoter hypermethylation in MLL-AF4-positive primary blasts and cell lines;upregulation of miRNA-143 expression by demethylation has therapeutic promise for MLL-AF4 B-cell ALL [76].

It is also important to consider that some miRNAs can behave as oncogenes in one cancer type and as tumor suppressive genes in others. It has been reported that miR-221 maintains a high expression in hepatic cancer and exerts an oncogenic function by targeting tumor suppressor PTEN, but this miRNA acts as a tumor suppressor in erythroblastic leukemia by inhibiting the KIT oncogene expression [77, 78]. Thus, identification of specific biological functions, type of cancer, and targets of miRNAs is a basic aspect when considering miRNA therapeutics.

8. Summary and future directions

Various studies have demonstrated that the oncomiRs or tumor suppressor miRNAs expression may significantly have potential how diagnostic and/or prognostic biomarkers, as well as monitoring the disease progression and in the response to treatment, and it may be a therapeutic target for treatment in ALL. Also, miRNAs expression levels may play an important role in the genesis and evolution of the ALL. Nevertheless, the biological effects and relevant target genes of many miRNAs that are deregulated and/or prognostically relevant in ALL need to be identified and characterized. Therefore, novel anti-ALL agents are needed to overcome chemotherapy resistance and reduce cytotoxicity. The mimics- and/or anti-miRNAs may be a good alternative. However, more experiments are required to evaluate the feasibility and safety of mimics- and/or anti-miRNAs in the clinical treatment.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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