Chapter

MicroRNAs and Their Role in Acute Lymphoblastic Leukemia

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Abstract

Acute lymphoblastic leukemia (ALL) has been established as the most common acute leukemia in children, accounting for 80–85% of cases. ALL occurs mostly in children and it is considered as a high-risk disease in the elderlies. ALL is characterized by a clonal disorder where the normal hematopoiesis is replaced by a malignant clonal expansion of lymphoid progenitors. Although many therapeutic strategies have been established to treat ALL leading to improved survival rates, the short-term and long-term complications derived from treatment toxicity represent a critical risk for patients. The treatment-related toxicity suggests a need for the development of new therapy strategies to effectively treat high-risk and low-risk disease. Nowadays, an important approach is focused on the identification of molecules involved in the mechanisms that lead to leukemia generation and progression to determine potential targets at the transcriptional level. MicroRNAs (miRNAs) are a group of key molecules that regulate signaling pathways related to lymphopoiesis. miRNAs participate in the regulation of hematopoietic differentiation and proliferation, as well as their activity. The present review details the recompilation of evidences about the relation between miRNAs and lymphopoiesis, ALL development and progression in order to propose and explore novel strategies to modulate ALL-related miRNA levels as a therapeutic approach.

Keywords: miRNAs, therapeutics, lymphopoiesis, acute lymphoblastic leukemia, agomiR, antagomiR

1. Acute lymphoblastic leukemia generalities

Acute lymphoblastic leukemia (ALL) has been established as the most common acute leukemia in children representing 80–85% of cases [1]. The global incidence ranges from three to five cases per 100, 000 population and the lowest incidence occurs in the adults older than 65 years old [2]. Even though ALL occurs mostly in children, it represents a devastating disease in the elderlies. ALL is a clonal disorder where the normal hematopoiesis is replaced by a malignant clonal expansion of lymphoid progenitors (blasts) [3]. Such clonal disorder is characterized by genetic abnormalities that lead to a block in B or T cell differentiation leading to abnormal cell proliferation and apoptosis in the bone marrow, peripheral blood and extramedullary sites [4, 5]. The overall survival of patients with ALL has been improved after treatment stratification according to immunophenotype and genotype. This treatment has allowed to incorporate, into therapy protocols, and more effective drug combinations [6]. Although improved survival rates have been obtained, the short-term and long-term complications derived from treatment toxicity represent

a critical risk for patients. This suggests a need for the development of new therapy strategies to diminish the treatment-related toxicity and effectively treat high-risk and low-risk disease. An important approach is focused on the mechanisms that lead to leukemia generation and progression by identifying potential targets at the transcriptional level.

The development of B-lymphocytes and T-lymphocytes from a lymphoid progenitor occurs in the bone marrow and thymus, respectively, and the normal lymphopoiesis is regulated at a transcriptional level involving transcription factors acting as regulators of genes expression [7]. Nevertheless, a question arises: does the transcriptional process is sufficient to control the cell fate, lineage and other aspects of cellular functioning? The answer is "no", and there are other key mechanisms involved. MicroRNAs (miRNAs) are a group of key molecules that regulate signaling pathways related to lymphopoiesis. miRNAs regulate hematopoietic differentiation and proliferation, as well as their activity. Besides, a deregulation in miRNAs expression is observed in leukemias having a main role in the pathogenesis of such clonal disorder [7, 8]. The first connection between miRNAs and leukemia indicated that 13q14 deletion in B-cell chronic lymphocytic leukemias induced the loss of miR-16-1 and miR-15a in 70% of chronic lymphocytic leukemias [9]. In addition, recent studies suggested that at least 50% of miRNAs are located in cancer-associated genomic regions and mRNAs are regulated by these miRNAs populations [5]. Moreover, different patterns of miRNAs are observed in normal lymphopoiesis and leukemias. The investigation of the relation between miRNAs and pathological cellular processes represents an interesting approach for the development of new therapeutic strategies.

2. miRNAs biology

miRNAs are endogenous small non-coding RNAs with a length of 19–25 nucleotides (nt) and their genes are transcribed by RNA polymerase II (Pol II) in the nucleus [10, 11]. miRNAs transcripts are first generated as pri-miRNAs structures (up to 1000 nt of length) which contain cap structures and poly-A tails (**Figure 1**). The pri-miRNAs transcript is briefly processed into precursor miRNA (pre-miRNA) transcript of 60–120 nt of length by the microprocessor complex formed by class 2 ribonuclease III enzyme called DROSHA and the DiGeorge Syndrome Critical Region Gene (DGCR8) protein. The pre-miRNA structure bears a hairpin structure with 2-nt overhang at the 3'end [12, 13]. The next step consists in exporting the pre-miRNA from the nucleus to the cytosol. This process is mediated by the exportin-5 (a RanGTP-dependent dsRNA-binding protein) which recognizes the overhang in the pre-miRNA as a target to be transported [14].

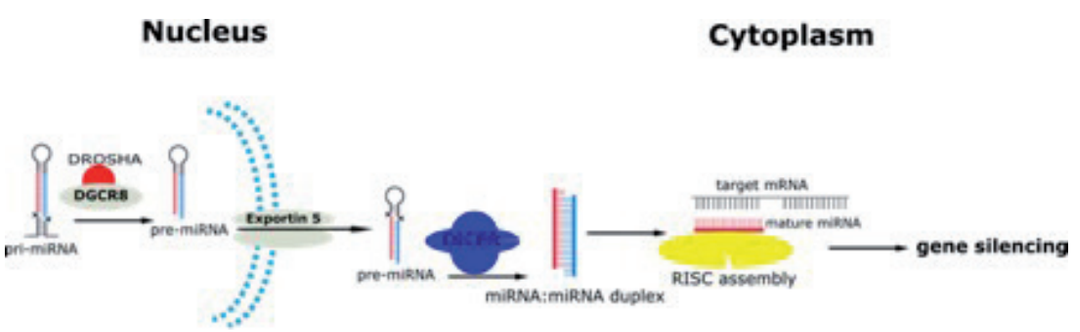

Figure 1.
miRNAs biogenesis and gene silencing mediated by miRNA.

Once in the cytosol, and pre-miRNA is processed by the DICER enzyme (RNAse type III) leading to a mature miRNA duplex (miRNA: miRNA) about 22 nt of length. The miRNA duplex is loaded into the RNA-induced silencing complex (RISC), composed by of the Argonaute2 (Ago2) and the trans-activator RNA (tar)-binding protein (TRBP). Note that the mature single-strand miRNA is retained by the Argo2 protein in the RISC complex to guide the gene silencing by binding to its mRNA target leading to mRNA degradation [10, 13, 15]. Recent evidence indicates that some pri-miRNAs contain open reading fragments about 300 nt and could be transported, without being processed, into the cytosol, and then become translated into micropeptides, having the ability to influence a variety of cellular processes. This is an additional field of opportunity to carry out functional studies with the aim to develop novel therapeutic strategies [16].

3. miRNAs and their implications in lymphopoiesis and ALL development

3.1 Lymphopoiesis regulation by miRNAs

Lymphopoiesis is a process in which hematopoietic stem cells (HSCs) differentiate into an immature form called lymphoid progenitor and finally into mature B- or T-lymphocytes [17]. The miRNAs play a key role in the process of cell differentiation by regulating several signaling pathways. The pattern of miRNAs expression is different according to normal or malignant lymphopoietic process.

The miRNA-150 (miR-150) is expressed in B- and T-cells and the lymphoid progenitors express the miR-150 to promote B-cell maturation and by assisting in the transition of the progenitor B-cells (pro-B) to precursor B-cell (pre-B) stage. When a premature miR-150 expression occurs, the result is a blocked transition from pro-B to pre-B stage [18, 19]. In the thymus, the expression of miR-150 enhances T-cell development and its key pathways (Notch pathway) and prevents an alternative lineage differentiation (B-cell differentiation) in the progenitors. Since C-myb is an essential transcription factor involved in the early lymphoid development, a downregulation eventually leads to an arrest from pro-B to pre-B stage. This event is accompanied by miR-150 overexpression [15, 17].

The miRNA-155 (miR-155) is upregulated in both B- and T-cells in their activated and mature stage. In the case of B-cells differentiation, miR-155 inhibits PU.1 expression leading to Pax5 downregulation and the initiation of the plasma cell differentiation pathway. This event is known as the miR-155-PU.1 axis. The role of miR-155 in T-cells differentiation depends on the level of miR-155 expression. The expression of miR-155 mediates the differentiation of T-cells into T-helper type 1, while its absence leads to T-cells transition into T-helper type [20, 21].

The miRNA-181 (miR-181) is a family of miRNAs and is composed of three clusters located in a different chromosome. Hsa-miR-181a-1 and hsa-miR181b-1 are located on chromosome 1; hsa-miR-181a-2 and hsa-miR181-b-2 are located on chromosome 9 and finally hsa-miR181c-1 and hsa-miR-181c-2 are located on chromosome19 [22]. miR-181 family have been reported to be implicated in lung and breast cancers [23]. miR-181a can act as inhibitor of the normal cellular response to DNA damage by affecting the expression and activity of the stress-sensor kinase ataxia telangiectasia mutated (ATM). In the early stage of B-cells differentiation, the expression of miR-181 is high and decreases subsequently within differentiation [17], and during T-cell development, the miR-181 is highly expressed in double-positive T-cells. The targets for miR-181 are BCL-2, CD89, EGR1 and T-cell receptor [24, 25].

miRNA	Function	Target	miRNA expression in ALL vs. normal samples	References
miR-150	Transition from pro-B to pre-B stage	C-MYB	High	He *et al*., 2015 [26]
miR-155	Promotes T-cell differentiation into Th type 1 cells	PTEN	High	Seddiki et al., 2014 [21]
miR-181	B-cell differentiation and T-cell development	BCL-2, MYC, CDX2, CD69, GR1, and T-cell receptor	High	Veruci et al., 2015 [24]
miR-17-92	Transition from pro-B to pre-B stage	YLD, HOXA9, BIM, RUNX1, MYC	High	Rao et al., 2015 [27]
miR-126	B-ALL development	MYC and CDX2	High	Fulci et al., 2009 [28]
miR-223	Reduction in cell growth and T-ALL development	IKAROS, PTEN, BIM, PHF6, NF1, and FBXW7	Low	Mavrakis et al., 2011 [29]
miR-19b	T-ALL development	IKAROS, PTEN, BIM, PHF6, NF1, and FBXW7	High	Mavrakis et al., 2011 [29]
miR-20a	T-ALL development	IKAROS, PTEN, BIM, PHF6, NF1, and FBXW7	High	Mavrakis et al., 2011 [29]
miR-92	T-ALL development	IKAROS, PTEN, BIM, PHF6, NF1, and FBXW7	High	Mavrakis et al., 2011 [29]
miR-26a	T-ALL development	KAROS, PTEN, BIM, PHF6, NF1, and FBXW7	High	Mavrakis et al., 2011 [29]
miR-123a	PI3K signaling activation	PTEN	High	Bertacchini et al., 2015 [30]
miR-21	Regulation of PI3K/Akt/ mTOR pathway	PTEN	High	Bertacchini et al., 2015 [30]
miR-99a	Promotes the differentiation of human granulocytes and monocytes cells	mTOR, IGF-1, and MCL1	Low	Li et al., 2012 [31], Li et al., 2013 [32]
miR-100	Promotes the differentiation of human granulocytes and monocytes cells	mTOR, IGF-1, and MCL1	Low	Li et al. 2013 [32]
miR-19	T-ALL development	PTEN, HOXA, CYLD, BIM, and NOTCH1	High	Tsuchida et al., 2011 [33]
miR-29a	T-ALL development	MYC and CDX2	Low	Zaidi et al., 2017 [34]
miR-30a	B-ALL development	NOTCH1, NOTCH2 and MYC	High	Ortega et al., 2015 [35]

Table 1.
Function, targets and expression level of miRNAs related to ALL.

The miR-17-92 cluster is composed of six miRNAs including miR-17, miR-18a, miR-19a, miR19-b-1, miR-20a and miR-92-1 and is highly expressed in both B- and T-lymphoid progenitors and subsequently decreases within maturation [27]. When miR-17-92 cluster is downregulated or absent, occurs B-cell differentiation disorder due to the overexpression of the proapoptotic protein BIM (target of miR-17-92 cluster). On the other hand, when miR-12-92 cluster is overexpressed during lymphopoiesis, promotes lymphoproliferative disorders and severe autoimmunity [36].

The aforementioned miRNAs play a critical role on the lymphopoiesis and the change of their expression pattern leads to blood disorders or malignant lymphopoiesis mechanisms. Such is the reason why miRNAs can be potential targets for treatment, diagnosis and prognosis in ALL.

3.2 The role of miRNAs in ALL development

Besides the involvement of aberrant miRNAs expression in malignant lymphopoiesis, it may be related to drug resistance mechanisms. Focusing on promoting the reversal expression of such miRNA may enhance disease management and improve clinical outcomes. By comparing miRNAs expression in both normal pediatric bone marrow and pediatric ALL, an overexpression of miR-100, miR-196b in ALL and lower expression of let-7e in normal bone marrow were reported [37]. In a study conducted in childhood B-ALL and T-ALL, the miRNA expression profile in the bone marrow was evaluated to discriminate between T-ALL and B-ALL. The results indicated a downregulation of 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 and upregulation of miR-450b-5p, miR-450a-5p, miR-542-5p, miR-424-5p, miR-629-5p, miR-29c-5p in T-ALL. Further machine process analyses showed that miR-29c-5p, involved in calcium signaling, is involved in B-cell fate and it is the best discriminator to stablish childhood B-ALL or T-ALL. In addition, clinical samples of T-ALL were studied and reveled that miR-223, miR-19b, miR-20a, miR-92, miR-142-3p, miR-150, miR-93, miR-26a, miR-16, and miR-342., miR-19b,-20a,-26a,-92 and miR-223 target T-ALL tumor suppressors, such as IKAROS, PTEN, BIM, PHF6, NF1 and FBXW7 [37], which means that overexpression of such miRNAs could lead to ALL development and represents a potential therapeutic target.

The identification of miRNAs that target genes of MYC, TFs of CDX2 and IncRNA of XIST could represent an approach to ALL therapeutics, due to that the aforementioned genes may play important role in the development of B-ALL. NOTCH1 is another important target due to mutations of gain of function, which are implicated in T-ALL development as well as NOTCH1 and NOTCH2 that take part in B-malignances [38]. **Table 1** exhibits a list of miRNAs involved in ALL development and pathogenesis considered as potential therapeutic targets.

4. Modulation of miRNAs expression levels in ALL: a therapeutic approach

Children diagnosed with ALL, in most cases follow a standard treatment protocol divided into three phases: induction, consolidation and maintenance, and sometimes a central nervous system-directed therapy. The drugs used in induction and consolidation phases usually include prednisolone (PRED), vincristine (VCR), L-asparaginase (L-ASP) and daunorubicin (DNR), all these drugs presents late effects. The maintenance phase is the most prolongated treatment in childhood ALL, however, it involves a much less intensive regimen than induction and consolidation phases. The maintenance phase has been demonstrated to lower the

risk of relapse, but could be a cause for emergence new mutations leading to drug resistance [16]. Even though the great effort in the development of new treatment strategies, drug resistance is the major cause of chemotherapy failure and relapse in pediatric patients. The classification of patients resistant or sensitive to drugs can be carried out based on the expression level of miRNAs.

The multidrug resistance (MDR) represents a problem in the treatment of pediatric ALL. It is considered an ubiquitous and severe clinical problem. MDR is mediated by adenosine triphosphate (ATP)-binding cassette (ABC) transporters. Several chemotherapeutic drugs are actively transported by ABC transporters across the cellular membranes leading to chemotherapy failure. Recent evidence indicates that some miRNAs tend to enhance chemotherapy response by modulating the expression of ABC transporters. In a study, the transfection of miR-326 into HepG2 cells demonstrated enhanced response to chemotherapeutic drugs due to downregulation of ABC transporter ABCC144 [16, 39]. Previous reports indicated that overexpression of ABCA2 and ABCA3 genes increases the risk of MDR and relapse in pediatric ALL patients [40]. Based upon bioinformatics analysis, miR-326 was identified as negative regulator of MDR-related genes, ABCA2 and ABCA3 in particular. Further evaluation of the miR-326 expression levels in pediatric ALL patients resistant to chemotherapy (MDR+) revealed that miR-326 is significantly decreased in MDR+ compared to the MDR- control group, supporting the idea that low level expression of miR-326 impacts directly on chemotherapy treatment response [41, 42].

Glucocorticoids (GC) are a group of drugs clinically used to treat ALL due to their involvement in cell progression, immunoglobulin, lymphokine production and apoptosis in immature lymphoblasts. The MLL rearrangements are common genetic abnormality in ALL. MLL-AF4 is the result of a balanced translocation between MLL and AF4 and it occurs in approximately 50% of ALL cases in infants. MLL-AF4 is an indicative of poor prognosis due to failure in GC-induced apoptosis. miR-128b and miR-221 are downregulated in this type of ALL and leads to overexpression of their targets: CDKN1B, MLL, AF4 and both MLL-AF4 and AF4-MLL fusion genes (involved in AL development). The restoration of miR-128b and miR-221 results in the downregulation of their aforementioned targets and increase the sensitivity to GC therapy [37, 43]. After transiently overexpression of miR-17 in a pre-B cell line (SUP-B15), it was found a reduced dexamethasone (DEX)-induced apoptosis indicating resistance to DEX. Further inhibition of miR-17 by locked nucleic acid inhibitor enhanced the response to DEX. The development of miRNA inhibitors, antagomiRs and agomiRs allows to modulate miRNAs levels in order to obtain a better response in ALL treatment.

AntagomiR is a chemically-modified single-strand miRNA inhibitor used to block miRNA regulation of target gene expression efficiently. AntagomiRs are synthesized to reduce the ability of endogenous miRNAs to silence target mRNA transcripts. They can downregulate the corresponding endogenous miRNAs by either local or systemic injection into the animals. Their structure consists of a single-strand RNA carrying the chemically modifications functioning by blocking a target of miRNA. The strand of the antagomiR has 2 phosphorothionates at the 5'end, 4 phosphorothionates, 1 cholesterol group at the 3'end and full-length nucleotide 2′-methoxy modification. Its stability is significantly higher than miRNA inhibitors. On the other hand, agomiR is a chemically-modified double-strand miRNA mimics which can mimic mature endogenous miRNAs after transfection into cells. They can upregulate the endogenous miRNA activity by utilizing the natural miRNA machinery. The antisense strand of the agomiR has 2 phosphorothionates at the 5'end, 4 phosphorothionates, 1 cholesterol group at the 3'end and full-length nucleotide 2′-methoxy modification. The chemically-modified structure

of agomiR increases its stability and activity. Both, agomiRs and antagomiRs are recommended for miRNA functional *in vitro* and *in vivo* studies.

Once a miRNA has been established or identified as a target to be downregulated, or up regulated, agomiRs or antagomiRs can be used to modulate miRNAs levels and further determination of anticancer effects. This is a promising and interesting approach to combine miRNA-based therapy and current chemotherapy to synergistically improve clinical outcomes. The potential therapeutic miRNAs targets described below can be modulated by using agomiR or antagomiR.

The miR-101 has a potential role in drug response to doxorubicin (DOXO) in Jurkat T-ALL. It was shown that miR-101 targets NOTCH1 which is linked to enhanced DOXO sensitivity to myeloma cell lines in mouse. Therefore, miR-101 may enhance DOXO-mediated apoptosis by repressing NOTCH1, while low expression of miR-101 may be related to chemoresistance in T-ALL [44].

For ALL patients with BCR-ABL fusion gene, the treatment with tyrosine-kinase inhibitors (TKI) could be a promising strategy even though the prognosis is suboptimal. BCR-ABL1 and ABL1 are direct targets of miR-203. However, miR-203 is silenced by genetic and epigenetic mechanisms in hematopoietic malignancies as leukemia. It has been reported that the restoration of miR-203 expression reduces BCR-ABL1 and ABL1 levels in cells and leads to arrest in cell proliferation [15, 45]. In addition, the inhibition of the DNMT3A gene, which gives the instructions for making the enzyme DNA methyltransferase alpha involved in DNA methylation and gene silencing, can be assessed by increasing miR-217 or mimics expression. This may prevent drug resistance to TKI in Philadelphia-chromosome-positive ALL patients, being another therapeutic strategy [46]. According to the aforementioned, the demethylation may be a potential therapeutic strategy in ALL. As mentioned before, the miR-143 is epigenetically repressed by promoter hypermethylation in MLL-AF4-positive primary blast, but not in normal bone marrow cells, and neither in MLL-AF4-negative primary blasts. Besides, MLL-AF4 expression is regulated by miR-143, such not being possible in MLL-AF4-positive cells. The restoration of miR-143 levels could induce apoptosis and regulate in a negative way the of the leukemia cells growth [47].

The miR-125b-2 cluster, consisting of miR-125b, miR-99a and let-7c, is increased in ETV6-RUNX1+ leukemia. According to previous reports, the miR-125b-2 cluster expression is not regulated by the ETV6-RUNX1 fusion protein, which indicates that the expression of this cluster may be an independent leukemia event. Further knockdown of miR-125b-2 cluster in the *ETV6-RUNX1*$^{+}$ cell line Reh led to increased cell sensitivity to DOXO and staurosporine treatment. Hence, the overexpression of miR-125b-2 cluster confers to leukemic cells survival advantage through the inhibition of apoptosis and failure in activation of caspase-3 [48]. These findings support the idea that miR-125b-2 cluster is a potential therapeutic target in pediatric ALL.

In pediatric ALL patients, a genome-wide miRNA analysis indicated a reduced miR-335 expression, such being the most significant miRNA abnormality associated with a poor outcome. Furthermore, the overexpression of miR-335 significantly sensitized the ALL cells to PRED. The role of miR-335 in PRED resistance was studied by investigating downstream pathways. The results suggested that low level of miR-335 leads to higher MAPK1-mediated survival. Further treatment with MEK/ERK inhibitor enhanced PRED-induced cell death suggesting that using synthetic miR-335 and overriding MAPK1 activity plus MEK/ERK pathway inhibition may provide a promising therapeutic strategy to overcome PRED resistance [49].

In regards of T-ALL, few studies investigate the role of miRNAs in GC response. GC bind to its receptor (GCR), which acts as a ligand-dependent-transcription factor, inducing cell cycle arrest and apoptosis in cancer cells [50]. The GCR is

modulated by miR-142-3p, which represses GCR biosynthesis. The inhibition of miR-142-3p in T-ALL cell lines resulted in increased GC-mediated cell death compared to not inhibited cells. Another protein involved in GC resistance via GCR repression is the FKBP51, which is negatively regulated by miR-100 and miR-99. Both miRNAs are found to be downregulated in the T-ALL as well as the B-ALL. In transfected T-ALL cell lines with mimics of miR-100 and miR-99, the result led to enhanced sensitivity to CG and apoptosis. In addition, previous studies reported that miR-100 and miR-99 act synergistically with miR-125 enhancing resistance to VCR [51, 52]. *In vitro* studies indicate that only the overexpression of the three aforementioned miRNAs led to VCR resistance. Moreover, hypoxia is a crucial microenvironmental factor supporting self-renewal of leukemic stem cells in bone marrow niches. miR-210 is one of the hypoxia-regulated miRNAs most studied in cancer including its role in drug resistance and as a prognostic potential. The miR-210 levels were modified in ETV6-RUNX+ Reh and MLL-AF4 + RS4; 11 pediatric ALL cell lines by introducing antagomiR and agomiR to miR-210. After 24 h of the transfection, both cell lines were treated with the DNR, VCR, DEX and L-ASP, individually or in combinations of the four drugs. In ETV6-RUNX+ Reh cells, the half maximal inhibitory concentrations (IC50s) of DNR, DEX and L-ASP were significantly decreased (in agomiR-transfected cells) or increased (in antagomiR-transfected cells) compared to cells transfected with negative control mimics. At the other extreme, the IC50s of DNR, DEX and VCR were decreased (in agomiR-transfected cells) or increased (in antagomiR-transfected cells) in MLL-AF4 + RS4;11 cells [53]. In regards with these findings, the use of agomiRs and antagomiRs to miRNAs could be an alternative to overcome resistance to chemotherapy. Nevertheless, the great challenge in clinical and nonclinical trials, is the delivery of synthetic miRNAs to leukemia cells effectively.

5. Conclusion and future directions

miRNAs are taking place as therapeutic targets promising in the molecular oncology due to their ability to regulate important cellular processes through multiple targets. Their inherent role in carcinogenesis can be as oncogenes or tumor suppressive genes, and the identification of specific biological functions, type of cancer and targets of miRNAs is a critical aspect in the approach of miRNAs therapeutics. Since miRNAs are differentially expressed in distinct stages of lymphopoiesis and influence ALL development, the aberrant miRNAs signatures observed in ALL may be intensively used to determine biomarkers for diagnosis, classification and prognosis. The changes in the expression level of several miRNAs play a functional role in drug resistance, and the reversal of such expression profiles could improve drug sensitivity to obtain better clinical outcomes. The transfection of agomiRs or antagomiRs to miRNAs allows the increase or decrease of specific miRNA expression levels. However, safety concerns and degradation effects limit their efficacy *in vivo*. There is a need for systemic delivery of miRNA as therapeutic agent in the treatment of ALL. The miRNAs listed before represent a low percentage of the total miRNAs studied as potential therapeutic targets. It is quite difficult to present the entire list, nonetheless, there is an available database considered as a valuable source of information for researchers to understand and investigate miRNAs and their targets with diagnostic and therapeutic potential in ALL. Such database is LeukmiR and can be consulted in this link http://tdb.ccmb.res.in/LeukmiR/

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