Review Article

ROLES AND CLINICAL IMPLICATIONS OF MicroRNAs IN ACUTE LYMPHOBLASTIC LEUKEMIA

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Abstract

MicroRNAs (miRNAs) are a class of small noncoding RNAs which regulate the expression of target genes by binding to messenger RNAs. miRNAs play a role in various biological processes, including proliferation, apoptosis and tumorigenesis. Dysregulation of miRNAs is implicated in invasion and metastasis in several human cancer types, and leukemia is not an exception.

Acute Lymphoblastic Leukemia (ALL) is an hematological malignancy characterized by the proliferation of early lymphoid precursors that replace normal hematopoietic cells of the bone marrow. The expression profiling of miRNAs in ALL could be used for the classification of the disease establishing specific diagnoses and offering prognostic values in the near future. The correlation of miRNAs dysregulation and biology of ALL demonstrates that specific miRNA may be a potential therapy target.

In this review we have focused our attention on the correlations between ALL and miRNAs, their link with signaling pathways and transcription factors in the disease and miRNA targeting therapeutic strategies with their advantages and potential use in clinical applications.

Contents:

Introduction

MicroRNAs (miRNAs), a new class of endogenous small noncoding RNAs, were originally identified as small non-coding RNAs that control the timing of larval development in Caenorhabditis elegans (Deb et al., 2017; Lee et al., 1993). They have subsequently been associated with several types of cancer (Bartel, 2004) and involved in various cellular processes, including DNA methylation, cellular growth, differentiation and apoptosis (Fabbri et al., 2007; Lima et al., 2017; Raji et al., 2017; Zhang et al., 2010). Their abnormal levels in tumors have important consequences since certain miRNAs overexpressed in tumors contribute to oncogenesis by tumor suppressors downregulation (Chen et al., 2016). The dysregulation of miRNAs has been reported in a variety of human cancers and hematological malignancies (Lu et al., 2005). In a microarray-based study it has been demonstrated that miRNAs expression correlates with both the type of leukemia and the prognosis of patients (Garzon and Croce, 2008; Mashreghi and Abolhassani, 2017).

Acute Lymphoblastic Leukemia (ALL) is a malignant disorder that originates from hematopoietic precursors of B- (80-85%) or T-cell (20-25%); the acquisition of a series of genetic aberrations leads to impaired maturation, with arrest of the differentiation process and abnormal proliferation. As a consequence, the accumulation of leukemic cells occurs in both the bone marrow, where it suppresses the physiologic hematopoiesis, and in extramedullary sites (Chiaretti et al., 2014).

ALL is most commonly a pediatric malignancy, but a significant percentage of cases occurs also in adults. Although pediatric ALL is highly responsive to chemotherapy, relapse occurs in approximately 25% of children (Pica et al., 2015). The majority of adults diagnosed with ALL relapse after treatment and their outlook is bleak, with further treatment including hematopoietic stem cell transplantation producing less than 10% overall survival at 5. In addition, the relatively non-specific actions of anti-cancer drugs often result in unacceptable toxicity that can occasionally prove to be fatal or produce lifelong consequences for survivors (Armstrong et al., 2007). The inability to further intensify current treatments in high-risk patients due to dose limiting toxicity means that new agents are required for further significant increases in overall survival (Wong et al., 2014).

miRNAs expressed differentially in distinct stages of lymphopoiesis, can hybridize with target messenger RNAs, regulating their post transcriptional expression, and influence the direction of lymphoid precursor maturation. In malignant lymphopoiesis there is an aberrant expression of

miRNAs involved and those aberrations can be used as signatures of different ALL subtypes. In addition, changes in the expression of several miRNAs may have functional relevance with leukemogenesis or drug resistance. As a result, reversal of the expression of these miRNAs may contrast the disease and improve clinical outcomes. However, among the studies of miRNAs, there are still some problems that need to be solved to understand the function of miRNAs in ALL more thoroughly (Luan et al., 2015). Recently, besides the immunophenotyping of ALL, an increasing number of studies showed that the miRNA expression profiles in acute leukemia have cooperative interactions in the development of leukemia. Therefore, the miRNA expression profile can be used as biomarkers in diagnosis, differential diagnosis, prognosis, and therapy of hematologic cancers (Li et al., 2014a; Tanaka et al., 2009; Wang et al., 2016).

1. miRNA discovery, biogenesis and function

miRNAs are small noncoding RNA molecules, ranging in length from 20 to 25 nucleotides, which primarily bind to the 3′ untranslated region (UTR) of messenger RNAs, resulting in a downregulation of target proteins through the degradation of this mRNA or through translational inhibition (Fig. 1) (Tye et al., 2015).

Pri-miRNA sequences are transcribed and cleaved within the nucleus to form the pre-miRNA transcript by the Microprocessor, which consists of RNase III enzyme Drosha and its partner protein DiGeorge Syndrome Critical Region Gene (DGCR8) (Mulrane et al., 2013; Zare-Maivan et al., 2017). The pre-miRNA is then exported to the cytoplasm by the nuclear export protein Exportin 5 (XPO5) (a RanGTP-dependent dsRNA-binding protein) where it is processed by Dicer, interacting with a trans-activator RNA (tar)-binding protein (TRBP) to produce short RNA duplexes (Zheng et al., 2017). These are loaded into an Argonaute protein (AGO2), which generates the effector complex RISC by dissociating the RNA duplex, leaving the single-stranded mature miRNA to guide gene silencing (Fig.1) (Deb et al., 2017). miRNAs sequences distribute throughout the whole genome and are classified as intergenic or intronic miRNA (Chen et al., 2013; Monteys et al., 2010). Currently, more than 24,000 miRNAs have been discovered, spanning more than 200 species including flora, fauna, and some microorganisms and more than 2,000 human mature miRNAs have been identified and reported in miRBase and miRBase Tracker (Van Peer et al., 2014; Weilner et al., 2015).

It has been demonstrated that miRNAs are frequently localized in common breakpoint regions related to tumors or in fragile sites, minimal regions of heterozygosity lost, and minimal amplification regions.

2. Involvement of miRNAs in lymphopoietic process

Hematopoiesis refers to the process that generates new, mature blood cells. All such cells derive from a single progenitor cell termed the Hematopoietic Stem Cell (HSC) which undergoes a process of highly regulated division and differentiation that produces the gamut of mature blood cells. Lymphopoiesis is the process in which B- and T-lymphocytes develop from progenitor cells. B-cell lymphopoiesis is completed in the bone marrow, whereas T-cell lymphopoiesis occurs in the thymus.

Nonetheless, their development and activation at the periphery are controlled by complex protein signaling pathways, which are regulated by the miRNAs (Johanson et al., 2014; Slavov et al., 2010). Several research groups described miRNA expression profile and/or function during the normal (and malignant) hematopoiesis in murine and humans (Hu and Li, 2016) suggesting that miRNAs are pivotal regulators of hematopoiesis implicated in regulating both the maintenance of the 'stemness' of the early progenitors and the various stages of differentiation to mature cells.

2.1 miR-150

miR-150 is expressed in both mature B- and T-cells. The lymphoid progenitors express miR-150 to give rise to mature B-cells and assist in the transition from progenitor B-cell (pro-B) to the precursor B-cell (pre-B) stage. Premature expression of miR-150 results in blocked transition from the pro-B-cell stage to the pre-B-cell stage (Havelange and Garzon, 2010; He et al., 2015). At variance, the expression of miR-150 in the thymus may enhance T-cell development and mechanisms, including upregulation of key pathways of T-cell development (like the Notch pathway) and suppression of alternative lineage differentiation (like B-cell differentiation) in progenitor cells (Ghisi et al., 2011). A confirmed target of miR-150 is c-Myb, an essential transcription factor involved in early lymphoid development. Its targeted loss in B-cells leads to the maturation arrest from pro-B to pre-B-cell stage, and, simultaneously, miR-150 is found to be overexpressed (Thomas et al., 2005; Xiao et al., 2007; Zhang et al., 2009).

2.2 miR-155

Recent data show the role of miR-155 in the differentiation of T-cells into different effectors T-helper (Th) cell subsets. miR-155 regulates the differentiation of T-cells into Th type 1 cells, and its absence results in the direct differentiation from T-cells to Th type 2 cells (O'Connell et al., 2010; Seddiki et al., 2014; Slavov et al., 2010; Thai et al., 2007; Zhang et al., 2009).

2.3 miR-181

Six members of the miR-181 family have been identified in the human genome, which include hsa-miR-181a-1and hsa-miR-181b-1 locate on chromosome 1; hsa-miR-181a-2 and hsa-miR-181b-2 locate on chromosome 9; as well as hsa-miR-181c and hsa-miR-181d locate on chromosome 19 (Yang et al., 2014).

miR-181 expression is high in the early B-cell differentiation stage and progressively decreases subsequently (Chen et al., 2004). In addition, miR-181 plays an important role in T-cell development and is highly expressed in double-positive T-cells (Zhang et al., 2009). BCL-2, CD69, EGR1and T-cell receptor are miR-181 targets, all involved in positive T-cell selection (Verduci et al., 2015).

2.4 miR-17-92 cluster

miR-17-92 cluster consists of six miRNAs: miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92-1, is highly expressed in the B- and T-lymphoid precursors and is decreased after maturation (Rao et al., 2015). As well as miR-150, absence of the cluster leads to the development of disorders in the maturation from pro-B to pre-B-cell stage, due to the increased levels of the pro-apoptotic protein BIM that is a target of the cluster(Havelange and Garzon, 2010). Studies by Rajewsky's group demonstrated that mice with targeted overexpression of the miR-17-92 cluster during lymphopoiesis develop severe lymphoproliferative disorders and autoimmunity (Xiao et al., 2008).

3. miRNA features related to ALL development

The aberrations in the expression of miRNAs involved in malignant lymphopoiesis, can be used as signatures of different ALL subtypes. Moreover, changes in the expression of several miRNAs may have functional relevance with leukemogenesis or drug resistance. As a result, the reversal of the expression of these miRNAs may alleviate the disease to some extent and improve clinical outcomes (Luan et al., 2015). Based on the relative expression of miR-148, miR-151, miR-424, miR-425-5p, miR-191, miR-146b, miR-128, miR-629 and miR-126, the B and T lineages of ALL can be distinguished (Zhang et al., 2009). Analysis of over 430 miRNAs in 50 clinical T-ALL samples have revealed a common signature: 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 223 have been shown to target T-ALL tumor suppressors such as IKAROS, PTEN, BIM, PHF6, NF1 and FBXW7 and lower expression of miR-223 has been reported in ALL cells isolated from pediatric patients and cell lines (Table 1). miR-612 and miR-499 have significant correlations with ALL susceptibility

(Mavrakis et al., 2011). Target gene of MYC, TFs of CDX2 and lncRNA of XIST may play important roles in the development of B-ALL, serving as a potential therapeutic target (Weng et al., 2006). Gain of function mutations in NOTCH1 are predominantly found in T-ALL, but recent evidence implicate NOTCH1 and NOTCH2 also in subsets of mature B-cell malignancies (Kridel et al., 2012; Martinez et al., 2014). Despite the fact that MYC is more prominently linked to B cell lymphoma biology, its relevance to T-ALL pathogenesis is well established, at least in part due to NOTCH1 ability to induce MYC expression (Klinakis et al., 2006; Weng et al., 2006). The miR-30 family represents a candidate for a putative MYC-dependent regulation of NOTCH1 and NOTCH2 expression. It has been confirmed that MYC negatively influences miR-30a expression and that this miRNA directly targets NOTCH1 and NOTCH2 (Schotte et al., 2009) (Table 1). Using genetic and pharmacological models, it has been characterized a regulatory loop, where by the MYC-mediated inhibition of miR-30a de-represses NOTCH, eventually modulating its own expression (Ortega et al., 2015).

4. ALL chromosomal abnormalities

It has been well recognized in B-ALL a set of genetic lesions, mostly represented by translocations and including BCR/ABL,ETV6/RUNX1,E2A/PBX1, and MLL rearrangements (Chiaretti et al., 2014). The hallmark of chronic myeloid leukemia (CML) is represented by the BCR/ABL rearrangement t(9;22) (q34;q11) (Ph chromosome) (Ciarcia et al., 2016) and it can also be detected in ALL (Kang et al., 2016). It induces constitutive activation of the ABL kinase, which in turns activates the mitogenic signaling pathways and induces altered cellular adhesion, inhibition of apoptosis, and proteasomal degradation of physiologically important cellular proteins, ultimately contributing to tumor growth and proliferation (Melo and Deininger, 2004; Sattler et al., 2003). The BCR/ABL oncogene has a very low frequency in childhood ALL, while it starts to increase during adolescence and reaches more than 50% among the elderly (Chiaretti et al., 2013). Until the introduction of tyrosine kinase inhibitors, the prognosis of these cases was poor and their use in clinical practice has profoundly changed the clinical management of these patients (Ottmann et al., 2007; Vignetti et al., 2007).

ETV6/RUNX1 is another kind of mutation but it is more frequent in children and virtually disappears with age progression (Harrison, 2009). It originates from t(12;21) (p13;q22) which creates a fusion gene including the 5′ portion of ETV6, a member of the ETS family of transcription factor genes, and almost the entire coding region of the transcription factor RUNX1 which encodes the α subunit of the core-binding factor, a master regulator of the formation of hematopoietic stem cells (Medina et al., 2016). As a result, the chimeric ETV6/RUNX1

transcription factor retains an essential protein-protein interaction domain of ETV6 and the DNA-binding and transcriptional regulatory sequences of RUNX1 (Loh and Rubnitz, 2002; Speck and Gilliland, 2002). Children with ETV6/RUNX1 rearrangement usually have excellent clinical outcomes.

In leukemias of B- and T-cell origin as well as in myeloid leukemias, the MLL gene can be disrupted, and so far about 100 partners have been recognized (Meyer et al., 2013; Meyer et al., 2009). The MLL fusion proteins have a dominant gain-of-function effect that enhances their transcriptional activity. These alterations mainly disrupt the normal pattern of expression of HOX genes, causing a change in the self-renewal and growth properties of hematopoietic stem cells and committed progenitors, thus eventually leading to leukemia (Corral et al., 1996; Dobson et al., 1999). In all cases, MLL rearrangements are associated with a very unfavorable outcome.

E2A/PBX1 rearrangement arises from t(1;19)(q23;p13)and is strongly associated with a pre-B immunophenotype as blasts usually express cytoplasmic immunoglobulins (Hunger, 1996).

The resulting protein induces cell differentiation arrest and tumor formation, most probably because of a reduction of the levels of wild-type E2Awhich eventually induce deregulation of lymphoid cell maturation and proliferation; furthermore, E2A/PBX1 itself induces the transcription activation of target genes. Its frequency is similar in children and adults, corresponding to 2-7%.

T-ALL is characterized by activating mutations of NOTCH1 and rearrangements of transcription factors TLX1 (HOX11), TLX3 (HOX11L2), LYL1, TAL1. Although these rearrangements are important initiating events in leukemogenesis and are widely used in diagnosis and risk stratification algorithms, they are insufficient to fully explain leukemogenesis. Rearrangements such as ETV6-RUNX1 are present years before the development of leukemia, and many of them do not alone result in the development of leukemia in experimental models. It is now known that the majority of ALL cases are characterized by distinct constellations of structural and submicroscopic genetic alterations and sequence mutations (Mullighan, 2012).

4.1 miRNA expression related to ALL chromosomal changes

Nearly three quarters of childhood ALL cases contain one or more total alterations of chromosome, with different immunophenotypes harboring different miRNA signatures (Li et al., 2014b; Mullighan, 2013). These signatures can help the diagnosis and classification of ALL (Luan et al., 2015). Compared with normal pediatric BM samples, miR-100 ($p<0.01$) and miR-196b ($p<0.01$) were expressed at a lower level in samples of pediatric ALL, whilst miR-128a ($p<0.01$) and miR-

181b ($p<0.01$) were overexpressed; miR-92a was similar for both groups (Table 1 and Table 2) (de Oliveira et al., 2012b). miRNA-100 was related to t(12; 21) positive ALL (de Oliveira et al., 2012a; Ohyashiki et al., 2010). B- and T-lineage ALL can be discriminated by the expression of miR-148, miR-151, and miR-424 by statistical analysis (ANOVA test). Indeed Macino's group first compared B-ALL versus T-ALL cases and found a few miRNAs whose expression differs between T-ALL and B-ALL (Fulci et al., 2009). Furthermore, B-lineage ALL subsets with special molecular lesions such as BCR/ABL, E2A/PBX1 and MLL/AF4, can be differentiated by a set of six miRNAs: miR-425-5p, miR-191, miR-146b, miR-128, miR-629, and miR-126as shown by statistical analysis performed by Macino's group. It has been observed differential expression patterns of ALL which were composed of several known miRNAs and 20 newly identified miRNAs that had first been discovered at the genomic level in human ALL (Zhang and Chen, 2009). These patterns constituted an ALL-specific miRNA signature for diagnosis.

A number of 118 single nucleotide polymorphisms (SNPs) has been analyzed in pre-miRNAs and miRNA-processing genes. A total of eleven SNPs, three SNPs present in miRNA genes (miR-612, miR-499, andmiR-449b*)* and eight present in six miRNA biogenesis pathway genes (TNRC6B, DROSHA, DGCR8, EIF2C1, CNOT1, and CNOT6) were significantly associated with ALL susceptibility. miR-612 and miR-499 had a more significant association with ALL susceptibility (Gutierrez-Camino et al., 2014).

In seven major subtypes of pediatric ALL (T-cell, MLL-rearranged, TEL-AML1-positive, E2A-PBX1-positive, hyperdiploid ALL, BCR-ABL-positive and "B-other" ALLs) miRNA expression levels have been compared. miR-708 was expressed from 250- to 6,500-fold higher in the 57 TEL-AML1, BCR-ABL, E2A-PBX1, hyperdiploid, and B-other cases than in the 20 MLL-rearranged and 15 T-ALL cases (Schotte et al., 2011). In 81 cases of pediatric ALL and 17 normal hematopoietic control cases it has been demonstrated the unique miRNA signatures of each subtype by analyzing the expression levels of 397 miRNAs. Additionally, the miRNA signature of TEL-AML1-positive and hyperdiploid cases overlapped partially, which may suggest a common underlying biology. It has been also reported that five miRNAs, miR-19b, miR-20a, miR-26a, miR-92, and miR-223, were identified as being capable of promoting T-ALL development in a mouse model and accounting for the majority of miRNA expression in human T-ALL, which could be used to reveal the pattern of gene interactions of T-ALL (Table 1) (Mavrakis et al., 2011).

5. Transcription factors in ALL

The development of functional lymphocytes is dependent on the maturation of multipotent progenitors (MPPs) in the bone marrow (BM). The formation of lineage-restricted progenitors is co-

coordinated by the action of transcription factors (TFs) that activate lineage-specific genes as well as restrict alternative cell fates. Considering the crucial roles for stage- and lineage-specific TFs such as PAX5, IKZF1 (IKAROS), TCF3 (E2A, TCFE2A), and EBF1 in the regulation of normal B-lymphocyte differentiation, it can be predicted that disruptions in the balanced action of these proteins represent an underlying cause of phenotypic features such as developmental arrest observed in B-lineage acute lymphoblastic leukemia (B-ALL) (Somasundaram et al., 2015). T-ALL is commonly associated with acquired chromosomal translocations and other genetic abnormalities, which lead to aberrant expression of a select group of transcription factors including HOX11/TLX1,TAL1/SCL, TAL2, LYL1,BHLHB1, LMO1, LMO2 and NOTCH1, resulting in their aberrant expression in developing thymocytes. Although the oncogenicity of these proteins is well established by several researchers in the past, the understanding of the downstream transcriptional programs that generate and maintain the T-ALL phenotype remains limited.

5.1 Role of miRNAs related to the transcription factors in ALL

Both the TFs and miRNAs are regulators of gene expression, and they may mutually regulate each other to form feedback loops, or they regulate the same target gene to form a feed-forward loop (FFL). It has been reported that hundreds of potential miRNA-mediated feedback and FFLs are available at the genome level (Re et al., 2009; Tsang et al., 2007). The hub genes are fragile points in the regulatory network with many nodes linked to them and mutation of them may deadly disrupt the normal function (Ye et al., 2012). In the miRNA-TF co-regulatory network, it has been identified four hub genes (CYLD, HOXA9, BCL2L11 and RUNX1) and four hub miRNAs (miR-19, miR-17, miR-92a-1 and miR-20a) in the miR-17–92 cluster, that likely play important regulatory roles in T-ALL. Meanwhile, it has been confirmed some well-studied T-ALL candidate genes (e.g. NOTCH1, PTEN, FBXW7 and LMO2) and nuclear TFs (e.g. CREB1, MYC, STAT and NF-κB) in the miRNA-TF network. Many of them are involved in important pathways, such as PI3K/AKT pathway, NOTCH pathway, NF-κB pathway and JAK pathway (Leung et al., 2008; Vilimas et al., 2007). As several groups have shown, miR-19 was significantly upregulated in Notch-induced T-ALL, and its target genes like PTEN, BCL2L11 (Bim) and NOTCH1 have been identified in mouse models (Mavrakis et al., 2010). It has been reported that deletion of the complete miR-17–92 cluster repressed the MYC-induced oncogenesis(Hong et al., 2010). This effect was rescued by reintroduction of the full cluster, but not by the cluster lacking miR-19. Recovery of miR-19 largely rescued the tumorigenicity, which identified miR-19 as the most important oncogenic miRNA in the miR-17–92 cluster (Olive et al., 2009). In T-ALL patients and

hematological malignant cell lines, miR-19 was significantly upregulated, and its target genes such as PTEN, HOXA, BCL2L11, CYLD and NOTCH1 were repressed.

6. PI3K/Akt/mTOR signaling pathway in ALL

Phosphoinositide 3-kinase, AKT, and mammalian target of rapamycin (mTOR) signaling pathway controls proliferation, differentiation, and survival processes of hematopoietic cells. Interest into targeting the PI3K/AKT/mTOR network in cancer has increased by the recent disclosure that PIK3CA of the PI3K pathway is the second most frequently mutated gene in cancer (Kandoth et al., 2013). Alterations of PI3K/AKT/mTOR are predominant in T-ALL with respect to other leukemia types.

In pediatric patients with pre-B-ALL, it has been shown that pAKT correlated with poor response to chemotherapy and overexpression of pAKT *in vitro* was enough to reverse the induction of apoptosis by standard anti-leukemic drugs (Evangelisti et al., 2011). Among other activated kinases, marked induction of mTOR signaling is present in CRLF2-rearranged B-ALL as measured by increased phosphorylation of pS6, 4EBP1 and eIF4e downstream of mTORC1. Pharmacological interruption of pathway elements of PI3K/mTOR abrogated target phosphorylation indicating a potential therapeutic window in this specific subgroup (Tasian et al., 2012).

6.1 miRNAs and their signature in PI3K signaling pathway in ALL

miRNAs are important regulators of key genes in the PI3K/Akt/mTOR pathway, suggesting miRNAs as a new therapeutic target also in leukemia (AlQurashi et al., 2013). It was shown in promyelocytic cell line NB4 that miR-223 is able to reduce cell growth by the inhibition of the insulin-like growth factor 1 receptor (IGF1-R), blocking PI3K signal (Jia et al., 2011) (Fig.2). Instead, miR-193-a is downregulated, determining the activation of the PI3K cascade, through the inhibition of the tumor suppressor PTEN (Schotte et al., 2009). miR-22 targets PTEN directly through a conserved site on the PTEN 3′UTR and it is upregulated by AKT, suggesting that miR-22 forms a feed-forward circuit in this pathway. A recent study revealed that miR-22 accelerated AKT activity upon growth factor stimulation, and attenuated its down regulation by serum withdrawal. Thus, in this regulatory network, miR-22 acts to enhance AKT signaling (Bar and Dikstein, 2010). Also miR-21 is involved in the regulation of PI3K/Akt/mTOR pathway and the expression of this miRNA is correlated to drug resistance by downregulation of PTEN (Bertacchini et al., 2015) (Fig.2). The three members of the miR-29 family, -a,-b and-c, function as tumor suppressor in different tumors, including leukemia (Zaidi et al., 2017; Zhang et al., 2009). The downregulation of miR-99-a and miR-110 is observed in ALL patients and their expression inhibit cell proliferation in

ALL cell lines. This inhibition is due by two prosurvival effectors such as mTOR and IGF-1 (Li et al., 2012) suggesting that these two miRNAs have different roles in myeloid cell and lymphocyte pathogenesis (Zhang and Chen, 2009). miR-100 and miR-99a overexpression inhibit IGF1R and mTOR and down-regulated MCL1 (Induced myeloid leukemia cell differentiation) (Schotte et al., 2009) (Fig. 2). This evidence suggested that miR-100 and miR-99a act as tumor suppressors and their restoration might be a possible therapeutic strategy for patients with ALL (de Oliveira et al., 2012b; Li et al., 2013). Finally, it has been also demonstrated that miR-221 negatively regulated PTEN by binding to its 3'UTR leading to inhibition of PTEN translation and activation of AKT pathway. Moreover, BCL-2, CCND1 and p27, downstream genes of pAKT, were regulated by miR-221 (Fig.2). therefore this miRNA is able to induce cell survival through targeting the PI3K/PTEN/AKT pathway and could be detected as a promising gene with its oncogene role (Zhao et al., 2013).

7. Role of miRNAs in ALL prognosis

miRNA signatures can be used not only in the diagnosis of the ALL, but also in their prognosis. Several miRNAs, involved in cell proliferation and apoptosis regulation, are implicated in leukemogenesis and they may interfere with either oncogenic or tumor-suppressor pathways influencing the prognosis of patients. Cellular miR-92a expression was significantly increased in a subset of ALL cells, and ALL patients with overexpression of miR-92a had poor prognoses (Table 1 and Table 2). Compared with peripheral blood mononuclear cells from healthy volunteers, the cell-to-plasma ratio of miR-92a expression was particularly higher in both ALL and AML cells (Table 1) (Ohyashiki et al., 2010).

It has also been suggested that expression level of miRNAs could be used as indicators of prognosis in children with ALL, such as higher expression of miR-128b at diagnosis predicted a better prognosis and prednisolon response (Nemes et al., 2015). A study of 147 patients with acute leukemia and 100 healthy individuals showed that acute leukemia (including both ALL and AML) patients with high miR-24 expression had shorter overall survival (Organista-Nava et al., 2015). In B- and T-ALL, patients with high miR-16 had a significantly shorter disease-free survival (DFS) (Kaddar et al., 2009). In another study the overall survival rate in miR-16 high-expression group decreased, thus showing a worst prognosis (Xiao et al., 2014).

8. Therapeutic implications of miRNAs in ALL

The recent advances in our understanding of the role of miRNAs in lymphoid malignancies demonstrate that miRNAs can effectively be used as tumor biomarkers with diagnostic, prognostic

and predictive-of-response-to-therapy implications (Fabbri and Croce, 2011). Glucocorticoids are used in the therapy of ALL and related malignancies and they are able to induce apoptosis in lymphoid lineage cells. However, a proportion of patients with ALL are insensitive to prednisone. It has been shown that eight miRNAs (miR-18a, miR-532, miR-218, miR-625, miR-193a, miR-638, miR-550, and miR-633) can help to distinguish the patients sensitive from those insensitive to prednisone (Xu et al., 2011).

Both miR-128b and miR-221 are downregulated in MLL-rearranged ALL and it has been hypothesized they may reduce GCs sensitivity (Kotani et al., 2010). ~~Restoration~~ Increase of miRNA-128b downregulates target genes including MLL, AF4, and their ~~both MLL-AF4, and AF4-MLL~~ fusion oncogenes, ~~and~~ whereas the ~~restoration~~ expression of miRNA-221 downregulates CDKN1B ~~cooperatively~~ CON CHI?. Thus, the sensitivity of two cultured lines of MLL-AF4 ALL cells to GCs is strengthened. In a subsequent study, researchers illustrated that one novel mutation of miR-128b significantly reduced its processing, and the resultant downregulation of mature miR-128b gave rise to GCs resistance due to the failure to downregulate the fusion oncogenes. By regulating miRNAs, therapeutic effect of GCs may be improved (Luan et al., 2015). ~~In a study by~~ Harada and colleagues in 2012 transiently overexpressed a miRNA precursor, pre-miRNA-17, in the pre-B ALL cell line (SUP-B15) ~~by electroporation~~ and monitored the dexamethasone-induced levels of apoptosis ~~using annexin/propidium iodide (PI) staining~~. They found that overexpression of PREmiRNA-17 reduced dexamethasone-induced cell death. On the contrary, ~~By~~ inhibition of miRNA-17 through locked nucleic acid (LNA) inhibitor, ~~to~~ increased dexamethasone sensitivity ~~was (Harada et al., 2012)~~.

2) ~~The human NR3C1 gene is encoded on chromosome 5q31.3 and consists of 9 exons~~ (Liang et al., 2017). 1) It has been found that miR-142-3p decreased NR3C1 protein expression and led to GC resistance by promoting T-leukemic cell proliferation but not apoptosis in ALL (Lv et al., 2012).

~~In a study,~~ Liang YN. et al., (ANNO) firstly reported in ALL that miR-124 also targeting NR3C1 could enhance the resistance of prednisone sensitive CCRF-CEM cells to dexamethasone and inhibits cell apoptosis, thus showing ~~by was~~ a similar ~~novel~~ mechanism for GC resistance. It was not clear~~ly~~ why miR-124 and miR-142-3p had different cell effects although they both targeted NR3C1.

For ALL with BCR-ABL fusion gene, the application of Tyrosine Kinase Inhibitors (TKI) may be a promising strategy, but the prognosis remains suboptimal (Faber et al., 2008). BCR-ABL1 and ABL1 are the direct targets of miR-203, which is silenced by genetic and epigenetic mechanisms in hematopoietic malignancies expressing either ABL1 or BCR-ABL1, and the restoration of miR-203

expression reduces ABL1 and BCR-ABL1 levels and inhibits cell proliferation (Bueno et al., 2008; Faber et al., 2008).

The inhibition of DNMT3A by forced expression of miR-217 may prevent drug resistance to TKI treatment in Philadelphia-chromosome-positive ALL patients. Hence, it may indicate another therapeutic strategy for BCR-ABL-positive ALL (Nishioka et al., 2014).

Demethylation could be a potential therapeutic strategy for ALL. In the MLL-AF4 ALL, miR-143 is epigenetically repressed by promoter hypermethylation in MLL-AF4-positive primary blasts and cell lines, but not in normal BM cells and MLL-AF4-negative primary blasts. Meanwhile, miR-143 was identified as a regulator of MLL-AF4 expression, and its restoration could induce apoptosis, negatively contributing to leukemia cell growth. Therefore, upregulation of miR-143 expression has therapeutic promise for MLL-AF4 B-cell ALL (Dou et al., 2012).

The *α* isoform of Protein kinase C (PKC*α*), has long been recognized as a regulator of tumor growth in ~~many kinds~~ a variety of cancers (Fang et al., 2016). ~~There has been a great in~~ Increasing interest targeting this kinase isoform for cancer therapy has developed. Targeting PKC*α*-mediated signal transduction ~~pathway~~ induces cell ~~killing~~ death in AML cells ~~by~~ inhibiting Bcl-2 phosphorylation and blocking ERK activation. Fang ZH. et al. (ANNO) showed that forced overexpression of miR-150 significantly repressed endogenous expression of PKC*α*, and luciferase reporter/mutagenesis assays confirmed that PRKCA is a transcriptional target of miR-150. Furthermore, they demonstrated that PKC*α* knockdown ~~expression~~ inhibited leukemia cell growth, supporting that PKC*α* is an essential target PER COSA? miR-150? and plays acritical role~~s~~ in miR-150-mediated antagonism to leukemic growth.

8.1 Current developments in hematological malignancies

~~Hematologic malignancies are among the top 10 malignant disorders with respect to the incidence as well as cause of death in patients suffering from cancers. They constitute approximately 9% of all tumor cases diagnosed in a year. Annual incidence rates of some of these cancers are consistently increasing. However, a trend of significant decline in mortality due to many hematological malignancies has been observed (Prakash et al., 2016). This positive trend is being observed predominantly because~~ numerous advances have been made in the field of hematological malignancies that have significantly improved the lives of patients with hematological disorders and blazed a trail for advances in other fields.

~~A powerful approach for treating hematological malignancies is allogeneic hematopoietic stem cell transplantation (allo-HSCT). Alloreactive T cells play a key role in de-bulking the patients' leukemia (Nelson and Paulos, 2015). However, a fatal complication of graft-versus-host disease~~

~~(GVHD) may be due T cells which target non-malignant tissues. Immunotherapists have invested time and effort to find alternative approaches to circumvent GVHD in patients. Recent advances in gene transfer technology demonstrate that the patient's T cells can be engineered with a chimeric antigen receptor (CAR) to recognize tumor antigen CD19 expressed on malignant cells (Brentjens et al., 2013).~~

Monoclonal antibodies (mAbs) that specifically recognize tumor antigens have been widely investigated. They are easy to produce, they are off-theshelf reagents with high protein stability and they can treat a wide range of patients with blood cancers. Most importantly, monoclonal antibodies, such as rituximab, alemtuzumab and trastuzumab, PATOLOGIE? have been widely used in patients and they are reported to mediate antitumor responses ~~in the clinic~~ (Weiner et al., 2010). Clinical trials suggest that hybrid antibodies (BiTEs) are promising for treating patients with hematologic malignancies. These artificial antibodies crosslink neoplastic T cells ~~with tumors and they are comprised of minimal binding domains of two distinct antibodies via a short peptide.~~ This kind of antibodies redirect cancer cell death via T cells at sub-picomolar concentrations, activate host T cells and drive a T cell's ability to serially kill tumor cells *in vivo*. This chain of events leads to the sustained activation, proliferation, and cytotoxicity of T cells as long as target cells are available (Nelson and Paulos, 2015). This effect capability has been successfully used in…….. CITARE 2-3 PATOLOGIE EMATOLOGICHE.

~~Cancer chemotherapy is one of the major medical advances of the 20th century. For certain hematological malignancies, such as ALL and subgroups of Hodgkin's (HL) and non-Hodgkin's lymphoma (NHL), chemotherapy can be curative and the promise of long-term survival makes the risk of adverse effects acceptable.~~

Targeted therapy is defined as a drug with a focused mechanism that specifically acts on a well-defined target or biological pathway that, when inactivated, causes regression or destruction of the malignant process. The obvious advantage of such therapies is that they are less toxic, with a higher therapeutic index and potentially more effective. Moreover, the application of these therapies is usually limited to patients known to carry the appropriate molecular target in their cancer cells, therefore eliminating the toxic and financial implications of more generalized use. While in some circumstances these new therapies will eliminate the need for traditional chemotherapy regimens QUALI?, in other cases it is likely that they will lower the threshold for induction of programmed cell death, thus enhancing the effectiveness of conventional chemotherapy approaches (Bahrami et al., 2017).

In the 1950_s the only treatment for CML was radiation of the spleen, granting patients about 30 months of survival. The identification of the mutation in the BCR-ABL caused by a specific

chromosomal translocation led to the development of imatinib, a gene-fusion-targeting drug that is the paradigm of a new generation of "smart" drugs. Imatinib is the first drug that has been designed to be so specific that it targets and corrects only the molecular defect that leads to CML, sparing patients most of the toxic side-effects that usually come with chemotherapy. Treated with this non-toxic oral drug, more than 75% of patients diagnosed with CML now achieve a durable complete cytogenetic remission. This development introduced a new way to think about treating cancer patients. With the disease in long-term remission (inactive, but not necessarily cured) many CML patients can now expect a normal life span.

Ibrutinib targets and inhibits the Bruton tyrosine kinase (BTK), a pathway that is deficient in X-linked a gammaglobulinemia, and critical for activation of ~~the protein kinase B (~~Akt~~)~~, extracellular receptor kinase, and nuclear factor (NF)-kB pathways. It is now Food and Drug Administration (FDA)- approved in the United States for treatment of chronic lymphocytic leukemia (CLL), relapsed mantle cell lymphoma (MCL), and Waldenström macroglobulinemia.

Phosphatidylinositol-3 kinases transmit intracellular signals critical for multiple cellular functions. Expression of the p110 delta isoform, targeted by idelalisib, is largely restricted to the hematopoietic lineage~~,~~ and has roles in signaling through the B-cell receptor CD40, the chemokine receptors CXC-chemokine receptor (CXCR)4 and CXCR5, B-cell activating factor receptor, integrins, and the IL-6 receptor. The putative involvement of these pathways in B-cell malignancies underlies the FDA indications of idelalisib as monotherapy for relapsed follicular B-cell non-Hodgkin lymphoma (NHL) and relapsed small lymphocytic lymphoma, and in combination with rituximab in relapsed CLL.

~~The B-cell leukemia/lymphoma-2 (BCL-2) protein??? was first identified as a fusion partner with IgH in follicular lymphomas carrying t(14;18) translocation.~~ The BCL-2 family proteins ~~share sequence similarities in the BCL-2 homology domains (BH1-4). They~~ are either anti-apoptotic, such as BCL-2, BCL-XL, MCL-1, BCL-W, BFL-1) or pro-apoptotic, such as BAX and BAK, by forming homo-or-heterodimers that regulate apoptosis in the mitochondria. ~~Pro-apoptotic members that share homology only in the BH3 domain induce apoptosis by interacting with other pro-apoptotic BCL2 proteins to release the activators or pro-apoptotic proteins.~~ There is concomitant expression, in cancer cells, of pro-apoptotic activators and anti-apoptotic proteins. It is the predominant function of the latter that prevents the cells from undergoing apoptosis, a condition known as BCL-2 addiction (Zhang et al., 2017). ???????????

Finally, the latest development in the field of Acute Leukemias is use of minimal residual disease (MRD) after induction therapy ~~for prognostication as well as~~ for prognostic evaluation and treatment planning. MRD is defined by residual leukemic cells following the achievement of

complete hematologic remission (Prakash et al., 2016). After more than a decade of research, MRD techniques appear finally ready to substitute morphological assessment of response in both experimental trials and the general clinical praxis and may benefit the most from miRNA analysys at the single cell level for precision and personalized medicine (Mosna et al., 2017).

9. Conclusions

miRNAs are important regulators of hematopoiesis and control the gene expression of several transcription factors essential for the commitment, differentiation, and apoptosis of hematopoietic stem cells (Bissels et al., 2012). A single miRNA targets many genes and it this matches the question whether or not targeting a single or multiple genes leads to hematological malignancies, as well as interfering with several pathways which are involved in disease development.

The identification of the molecular effectors mediating the effects of the miRNome de-regulation on the development of malignancy is undergoing, and suggests potential new strategies to overcome such aberrations. Moreover, for new promising therapeutic implications, these discoveries have clearly demonstrated that miRNAs can also serve as molecular biomarkers of cancer with prognostic implications and as predictive biomarkers of response to treatment. It is likely that in the next few years, new miRNA-based diagnostic, prognostic and predictive kits will be available for clinicians and miRNA-derived treatments will begin their clinical trial journey towards the development of new clinical agents.

Figure Legend

Figure 1. miRNA biogenesis and mechanism of action. miRNA biogenesis begins inside the nucleus, then its processing and maturation take place in the cytoplasm of an eukaryotic cell.

Figure 2. The effect of miRNA-mediated PI3K/Akt/mTOR signaling on leukemias. Scheme of the effector miRNAs and PI3K/Akt/mTOR pathway inhibitors in different leukemias. miR-21 and miR-22 are activator miRNA, and miR-99a, miR-100, miR-193a and miR-223 are inhibitor miRNA of the PI3K/Akt/mTOR pathway**.**

Conflict of interest

The authors declare that they have no conflict of interest.

References

AlQurashi N, Hashimi SM, Wei MQ. 2013. Chemical Inhibitors and microRNAs (miRNA) Targeting the Mammalian Target of Rapamycin (mTOR) Pathway: Potential for Novel Anticancer Therapeutics. Int J Mol Sci 14(2):3874-3900.

Armstrong GT, Sklar CA, Hudson MM, Robison LL. 2007. Long-term health status among survivors of childhood cancer: Does sex matter? Journal of Clinical Oncology 25(28):4477-4489.

Bahrami A, Khazaei M, Bagherieh F, Ghayour-Mobarhan M, Maftouh M, Hassanian SM, Avan A. 2017. Targeting stroma in pancreatic cancer: Promises and failures of targeted therapies. Journal of cellular physiology 232(11):2931-2937.

Bar N, Dikstein R. 2010. miR-22 Forms a Regulatory Loop in PTEN/AKT Pathway and Modulates Signaling Kinetics. PloS one 5(5).

Bartel DP. 2004. MicroRNAs: Genomics, biogenesis, mechanism, and function. Cell 116(2):281-297.

Bertacchini J, Heidari N, Mediani L, Capitani S, Shahjahani M, Ahmadzadeh A, Saki N. 2015. Targeting PI3K/AKT/mTOR network for treatment of leukemia. Cell Mol Life Sci 72(12):2337-2347.

Bissels U, Bosio A, Wagner W. 2012. MicroRNAs are shaping the hematopoietic landscape. Haematol-Hematol J 97(2):160-167.

Brentjens RJ, Davila ML, Riviere I, Park J, Wang XY, Cowell LG, Bartido S, Stefanski J, Taylor C, Olszewska M, Borquez-Ojeda O, Qu JR, Wasielewska T, He Q, Bernal Y, Rijo IV, Hedvat C, Kobos R, Curran K, Steinherz P, Jurcic J, Rosenblat T, Maslak P, Frattini M, Sadelain M. 2013. CD19-Targeted T Cells Rapidly Induce Molecular Remissions in Adults with Chemotherapy-Refractory Acute Lymphoblastic Leukemia. Sci Transl Med 5(177).

Bueno MJ, Perez de Castro I, de Cedron MG, Santos J, Calin GA, Cigudosa JC, Croce CM, Fernandez-Piqueras J, Malumbres M. 2008. Genetic and epigenetic silencing of microRNA-203 enhances ABL1 and BCR-ABL1 oncogene expression. Cancer cell 13(6):496-506.

Chen CZ, Li L, Lodish HF, Bartel DP. 2004. MicroRNAs modulate hematopoietic lineage differentiation. Science 303(5654):83-86.

Chen YC, Chen BC, Yu CC, Lin SH, Lin CH. 2016. miR-19a,-19b, and-26b Mediate CTGF Expression and Pulmonary Fibroblast Differentiation. Journal of cellular physiology 231(10):2236-2248.

Chen Z, Hu Z, Lu ZQ, Cai SY, Gu XX, Zhuang HX, Ruan ZH, Xia ZY, Irwin MG, Feng D, Zhang LQ. 2013. Differential MicroRNA Profiling in a Cellular Hypoxia Reoxygenation Model upon Posthypoxic Propofol Treatment Reveals Alterations in Autophagy Signaling Network. Oxid Med Cell Longev.

Chiaretti S, Brugnoletti F, Tavolaro S, Bonina S, Paoloni F, Marinelli M, Patten N, Bonifacio M, Kropp MG, Sica S, Guarini A, Foa R. 2013. TP53 mutations are frequent in adult acute lymphoblastic leukemia cases negative for recurrent fusion genes and correlate with poor response to induction therapy. Haematologica 98(5):E59-E61.

Chiaretti S, Gianfelici V, Ceglie G, Foa R. 2014. Genomic Characterization of Acute Leukemias. Med Prin Pract 23(6):487-506.

Ciarcia R, Damiano S, Puzio MV, Montagnaro S, Pagnini F, Pacilio C, Caparrotti G, Bellan C, Garofano T, Polito MS, Giordano A, Florio S. 2016. Comparison of Dasatinib, Nilotinib, and Imatinib in the Treatment of Chronic Myeloid Leukemia. Journal of cellular physiology 231(3):680-687.

Corral J, Lavenir I, Impey H, Warren AJ, Forster A, Larson TA, Bell S, McKenzie ANJ, King G, Rabbitts TH. 1996. An MII-AF9 fusion gene made by homologous recombination causes acute leukemia in chimeric mice: A method to create fusion oncogenes. Cell 85(6):853-861.

de Oliveira JC, Brassesco MS, Scrideli CA, Tone LG, Narendran A. 2012a. MicroRNA expression and activity in pediatric acute lymphoblastic leukemia (ALL). Pediatric blood & cancer 59(4):599-604.

de Oliveira JC, Scrideli CA, Brassesco MS, Morales AG, Pezuk JA, Queiroz RD, Yunes JA, Brandalise SR, Tone LG. 2012b. Differential MiRNA expression in childhood acute lymphoblastic leukemia and association with clinical and biological features. Leukemia research 36(3):293-298.

Deb B, Debnath S, Deb A, Maiti DK, Majumdar S. 2017. Copper nanoparticles catalyzed N-H functionalization: An efficient solvent-free N-tert-butyloxycarbonylation strategy. Tetrahedron Lett 58(7):629-633.

Dobson CL, Warren AJ, Pannell R, Forster A, Lavenir I, Corral J, Smith AJH, Rabbitts TH. 1999. The MII-AF9 gene fusion in mice controls myeloproliferation and specifies acute myeloid leukaemogenesis. Embo Journal 18(13):3564-3574.

Dou L, Zheng D, Li J, Li Y, Gao L, Wang L, Yu L. 2012. Methylation-mediated repression of microRNA-143 enhances MLL-AF4 oncogene expression. Oncogene 31(4):507-517.

Evangelisti C, Ricci F, Tazzari P, Chiarini F, Battistelli M, Falcieri E, Ognibene A, Pagliaro P, Cocco L, McCubrey JA, Martelli AM. 2011. Preclinical testing of the Akt inhibitor triciribine in T-cell acute lymphoblastic leukemia. Journal of cellular physiology 226(3):822-831.

Fabbri M, Croce CM. 2011. Role of microRNAs in lymphoid biology and disease. Curr Opin Hematol 18(4):266-272.

Fabbri M, Ivan M, Cimmino A, Negrini M, Calin GA. 2007. Regulatory mechanisms of microRNAs involvement in cancer: the strange case of Dr Jekyll and Mr Hyde. Expert Opin Biol Th 7(7):1009-1019.

Faber J, Gregory RI, Armstrong SA. 2008. Linking miRNA regulation to BCR-ABL expression: The next dimension. Cancer cell 13(6):467-469.

Fang ZH, Wang SL, Zhao JT, Lin ZJ, Chen LY, Su R, Xie ST, Carter BZ, Xu B. 2016. miR-150 exerts antileukemia activity in vitro and in vivo through regulating genes in multiple pathways. Cell Death Dis 7.

Fulci V, Colombo T, Chiaretti S, Messina M, Citarella F, Tavolaro S, Guarini A, Foa R, Macino G. 2009. Characterization of B- and T-Lineage Acute Lymphoblastic Leukemia by Integrated Analysis of MicroRNA and mRNA Expression Profiles. Gene Chromosome Canc 48(12):1069-1082.

Garzon R, Croce CM. 2008. MicroRNAs in normal and malignant hematopoiesis. Curr Opin Hematol 15(4):352-358.

Ghisi M, Corradin A, Basso K, Frasson C, Serafin V, Mukherjee S, Mussolin L, Ruggero K, Bonanno L, Guffanti A, De Bellis G, Gerosa G, Stellin G, D'Agostino DM, Basso G, Bronte V, Indraccolo S, Amadori A, Zanovello P. 2011. Modulation of microRNA expression in human T-cell development: targeting of NOTCH3 by miR-150. Blood 117(26):7053-7062.

Gutierrez-Camino A, Lopez-Lopez E, Martin-Guerrero I, de Andoin NG, Navajas A, Garcia-Miguel P, Baneres AC, Garcia-Orad A. 2014. New Susceptibility Markers in Pediatric Acute Lymphoblastic Leukemia: Non Coding Rnas. Pediatric blood & cancer 61:S258-S258.

Harada M, Pokrovskaja-Tamm K, Soderhall S, Heyman M, Grander D, Corcoran M. 2012. Involvement of miR17 pathway in glucocorticoid-induced cell death in pediatric acute lymphoblastic leukemia. Leukemia & lymphoma 53(10):2041-2050.

Harrison CJ. 2009. Cytogenetics of paediatric and adolescent acute lymphoblastic leukaemia. British journal of haematology 144(2):147-156.

Havelange V, Garzon R. 2010. MicroRNAs: Emerging Key Regulators of Hematopoiesis. Am J Hematol 85(12):935-942.

He Y, Chevillet JR, Liu G, Kim TK, Wang K. 2015. The effects of microRNA on the absorption, distribution, metabolism and excretion of drugs. Brit J Pharmacol 172(11):2733-2747.

Hong LX, Lai MY, Chen M, Xie CC, Liao R, Kang YJ, Xiao CC, Hu WY, Han JH, Sun PQ. 2010. The miR-17-92 Cluster of MicroRNAs Confers Tumorigenicity by Inhibiting Oncogene-Induced Senescence. Cancer research 70(21):8547-8557.

673 Hu YG, Li SG. 2016. Survival regulation of leukemia stem cells. Cell Mol Life Sci 73(5):1039-
674 1050.
675 Hunger SP. 1996. Chromosomal translocations involving the E2A gene in acute lymphoblastic
676 leukemia: Clinical features and molecular pathogenesis. Blood 87(4):1211-1224.
677 Jia CY, Li HH, Zhu XC, Dong YW, Fu D, Zhao QL, Wu W, Wu XZ. 2011. MiR-223 Suppresses
678 Cell Proliferation by Targeting IGF-1R. PloS one 6(11).
679 Johanson TM, Skinner JPJ, Kumar A, Zhan YF, Lew AM, Chong MMW. 2014. The role of
680 microRNAs in lymphopoiesis. Int J Hematol 100(3):246-253.
681 Kaddar T, Rouault JP, Chien WW, Chebel A, Gadoux M, Salles G, Ffrench M, Magaud JP. 2009.
682 Two new miR-16 targets: caprin-1 and HMGA1, proteins implicated in cell proliferation.
683 Biol Cell 101(9):511-524.
684 Kandoth C, McLellan MD, Vandin F, Ye K, Niu BF, Lu C, Xie MC, Zhang QY, McMichael JF,
685 Wyczalkowski MA, Leiserson MDM, Miller CA, Welch JS, Walter MJ, Wendl MC, Ley
686 TJ, Wilson RK, Raphael BJ, Ding L. 2013. Mutational landscape and significance across 12
687 major cancer types. Nature 502(7471):333-+.
688 Kang ZJ, Liu YF, Xu LZ, Long ZJ, Huang D, Yang Y, Liu B, Feng JX, Pan YJ, Yan JS, Liu QT.
689 2016. The Philadelphia chromosome in leukemogenesis. Chin J Cancer 35.
690 Klinakis A, Szaboics M, Politi K, Kiaris H, Artavanis-Tsakonas S, Efstratiadis A. 2006. Myc is a
691 Notch1 transcriptional target and a requisite for Notch1-induced mammary tumorigenesis in
692 mice. Proceedings of the National Academy of Sciences of the United States of America
693 103(24):9262-9267.
694 Kotani A, Harnprasopwat R, Toyoshima T, Kawamata T, Tojo A. 2010. miRNAs in normal and
695 malignant B cells. Int J Hematol 92(2):255-261.
696 Kridel R, Sehn LH, Gascoyne RD. 2012. Pathogenesis of follicular lymphoma. Journal of Clinical
697 Investigation 122(10):3424-3431.
698 Lee RC, Feinbaum RL, Ambros V. 1993. The C-Elegans Heterochronic Gene Lin-4 Encodes Small
699 Rnas with Antisense Complementarity to Lin-14. Cell 75(5):843-854.
700 Leung KT, Li KKH, Sun SSM, Chan PKS, Ooi VEC, Chiu LCM. 2008. Activation of the JNK
701 pathway promotes phosphorylation and degradation of Bim(EL) - a novel mechanism of
702 chemoresistance in T-cell acute lymphoblastic leukemia. Carcinogenesis 29(3):544-551.
703 Li QH, Pan ZF, Wang XJ, Gao ZQ, Ren CN, Yang WW. 2014a. miR-125b-1-3p inhibits
704 trophoblast cell invasion by targeting sphingosine-1-phosphate receptor 1 in preeclampsia.
705 Biochemical and biophysical research communications 453(1):57-63.
706 Li WY, Chen XM, Xiong W, Guo DM, Lu L, Li HY. 2014b. Detection of Microvesicle miRNA
707 Expression in ALL Subtypes and Analysis of Their Functional Roles. J Huazhong U Sci-
708 Med 34(5):640-645.
709 Li XJ, Luo XQ, Han BW, Duan FT, Wei PP, Chen YQ. 2013. MicroRNA-100/99a, deregulated in
710 acute lymphoblastic leukaemia, suppress proliferation and promote apoptosis by regulating
711 the FKBP51 and IGF1R/mTOR signalling pathways. British journal of cancer 109(8):2189-
712 2198.
713 Li Y, Hu ZT, Chen B, Bu Q, Lu WJ, Deng Y, Zhu RM, Shao X, Hou J, Zhao JX, Li HY, Zhang BL,
714 Huang YN, Lv L, Zhao YL, Cen XB. 2012. Taurine attenuates methamphetamine-induced
715 autophagy and apoptosis in PC12 cells through mTOR signaling pathway. Toxicol Lett
716 215(1):1-7.
717 Liang YN, Tang YL, Ke ZY, Chen YQ, Luo XQ, Zhang H, Huang LB. 2017. MiR-124 contributes
718 to glucocorticoid resistance in acute lymphoblastic leukemia by promoting proliferation,
719 inhibiting apoptosis and targeting the glucocorticoid receptor. J Steroid Biochem 172:62-68.
720 Lima TI, Araujo HN, Menezes ES, Sponton CH, Araujo MB, Bomfim LHM, Queiroz AL, Passos
721 MA, Sousa TAE, Hirabara SM, Martins AR, Sampaio HCLB, Rodrigues A, Curi R,
722 Carneiro EM, Boschero AC, Silveira LR. 2017. Role of microRNAs on the Regulation of

723 Mitochondrial Biogenesis and Insulin Signaling in Skeletal Muscle. Journal of cellular
724 physiology 232(5):958-966.
725 Loh ML, Rubnitz JE. 2002. TEL/AML1-positive pediatric leukemia: prognostic significance and
726 therapeutic approaches. Curr Opin Hematol 9(4):345-352.
727 Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, Sweet-Cordero A, Ebet BL, Mak
728 RH, Ferrando AA, Downing JR, Jacks T, Horvitz HR, Golub TR. 2005. MicroRNA
729 expression profiles classify human cancers. Nature 435(7043):834-838.
730 Luan CX, Yang ZX, Chen BA. 2015. The functional role of microRNA in acute lymphoblastic
731 leukemia: relevance for diagnosis, differential diagnosis, prognosis, and therapy.
732 Oncotargets Ther 8:2903-2914.
733 Lv M, Zhang X, Jia H, Li D, Zhang B, Zhang H, Hong M, Jiang T, Jiang Q, Lu J, Huang X, Huang
734 B. 2012. An oncogenic role of miR-142-3p in human T-cell acute lymphoblastic leukemia
735 (T-ALL) by targeting glucocorticoid receptor-alpha and cAMP/PKA pathways. Leukemia
736 26(4):769-777.
737 Martinez N, Almaraz C, Vaque JP, Varela I, Derdak S, Beltran S, Mollejo M, Campos-Martin Y,
738 Agueda L, Rinaldi A, Kwee I, Gut M, Blanc J, Oscier D, Strefford JC, Martinez-Lopez J,
739 Salar A, Sole F, Rodriguez-Peralto JL, Diez-Tascon C, Garcia JF, Fraga M, Sebastian E,
740 Alves J, Menarguez J, Gonzalez-Carrero J, Casado LF, Bayes M, Bertoni F, Gut I, Piris
741 MA. 2014. Whole-exome sequencing in splenic marginal zone lymphoma reveals mutations
742 in genes involved in marginal zone differentiation. Leukemia 28(6):1334-1340.
743 Mashreghi M, Abolhassani B. 2017. A Cluster-Based Cooperative Spectrum Sensing Strategy to
744 Maximize Achievable Throughput. Wireless Pers Commun 96(3):4557-4584.
745 Mavrakis KJ, Van der Meulen J, Wolfe AL, Liu XP, Mets E, Taghon T, Khan AA, Setty M,
746 Rondou P, Vandenberghe P, Delabesse E, Benoit Y, Socci NB, Leslie CS, Van Vlierberghe
747 P, Speleman F, Wendel HG. 2011. A cooperative microRNA-tumor suppressor gene
748 network in acute T-cell lymphoblastic leukemia (T-ALL) (vol 43, pg 673, 2011). Nature
749 genetics 43(8):815-815.
750 Mavrakis KJ, Wolfe AL, Oricchio E, Palomero T, de Keersmaecker K, McJunkin K, Zuber J, James
751 T, Khan AA, Leslie CS, Parker JS, Paddison PJ, Tam W, Ferrando A, Wendel HG. 2010.
752 Genome-wide RNA-mediated interference screen identifies miR-19 targets in Notch-
753 induced T-cell acute lymphoblastic leukaemia. Nature cell biology 12(4):372-379.
754 Medina MA, Ugarte GD, Vargas MF, Avila ME, Necunir D, Elorza AA, Gutierrez SE, De Ferrari
755 GV. 2016. Alternative RUNX1 Promoter Regulation by Wnt/beta-Catenin Signaling in
756 Leukemia Cells and Human Hematopoietic Progenitors. Journal of cellular physiology
757 231(7):1460-1467.
758 Melo JV, Deininger MWN. 2004. Biology of chronic myelogenous leukemia-signaling pathways of
759 initiation and transformation. Hematol Oncol Clin N 18(3):545-+.
760 Meyer C, Hofmann J, Burmeister T, Groger D, Park TS, Emerenciano M, de Oliveira MP,
761 Renneville A, Villarese P, Macintyre E, Cave H, Clappier E, Mass-Malo K, Zuna J, Trka J,
762 De Braekeleer E, De Braekeleer M, Oh SH, Tsaur G, Fechina L, van der Velden VHJ, van
763 Dongen JJM, Delabesse E, Binato R, Silva MLM, Kustanovich A, Aleinikova O, Harris
764 MH, Lund-Aho T, Juvonen V, Heidenreich O, Vormoor J, Choi WWL, Jarosova M,
765 Kolenova A, Bueno C, Menendez P, Wehner S, Eckert C, Talmant P, Tondeur S, Lippert E,
766 Launay E, Henry C, Ballerini P, Lapillone H, Callanan MB, Cayuela JM, Herbaux C,
767 Cazzaniga G, Kakadiya PM, Bohlander S, Ahlmann M, Choi JR, Gameiro P, Lee DS,
768 Krauter J, Cornillet-Lefebvre P, Kronnie GT, Schafer BW, Kubetzko S, Alonso CN, Stadt
769 UZ, Sutton R, Venn NC, Izraeli S, Trakhtenbrot L, Madsen HO, Archer P, Hancock J,
770 Cerveira N, Teixeira MR, Lo Nigro L, Moricke A, Stanulla M, Schrappe M, Sedek L,
771 Szczepanski T, Zwaan CM, Coenen EA, van den Heuvel-Eibrink MM, Strehl S, Dworzak
772 M, Panzer-Grumayer R, Dingermann T, Klingebiel T, Marschalek R. 2013. The MLL
773 recombinome of acute leukemias in 2013. Leukemia 27(11):2165-2176.

Meyer C, Kowarz E, Hofmann J, Renneville A, Zuna J, Trka J, Ben Abdelali R, Macintyre E, De Braekeleer E, De Braekeleer M, Delabesse E, de Oliveira MP, Cave H, Clappier E, van Dongen JJM, Balgobind BV, van den Heuvel-Eibrink MM, Beverloo HB, Panzer-Grumayer R, Teigler-Schlegel A, Harbott J, Kjeldsen E, Schnittger S, Koehl U, Gruhn B, Heidenreich O, Chan LC, Yip SF, Krzywinski M, Eckert C, Moricke A, Schrappe M, Alonso CN, Schafer BW, Krauter J, Lee DA, zur Stadt U, Kronnie GT, Sutton R, Izraeli S, Trakhtenbrot L, Lo Nigro L, Tsaur G, Fechina L, Szczepanski T, Strehl S, Ilencikova D, Molkentin M, Burmeister T, Dingermann T, Klingebiel T, Marschalek R. 2009. New insights to the MLL recombinome of acute leukemias. Leukemia 23(8):1490-1499.

Monteys AM, Spengler RM, Wan J, Tecedor L, Lennox KA, Xing Y, Davidson BL. 2010. Structure and activity of putative intronic miRNA promoters. Rna 16(3):495-505.

Mosna F, Capelli D, Gottardi M. 2017. Minimal Residual Disease in Acute Myeloid Leukemia: Still a Work in Progress? J Clin Med 6(6).

Mullighan CG. 2012. Sequencing the genome of acute lymphoblastic leukemia. Cancer research 72.

Mullighan CG. 2013. Recent Insights into the Biology of ALL from Next-Generation Sequencing. Ann Hematol 92:S54-S54.

Mulrane L, McGee SF, Gallagher WM, O'Connor DP. 2013. miRNA Dysregulation in Breast Cancer. Cancer research 73(22):6554-6562.

Nelson MH, Paulos CM. 2015. Novel immunotherapies for hematologic malignancies. Immunol Rev 263(1):90-105.

Nemes K, Csoka M, Nagy N, Mark A, Varadi Z, Danko T, Kovacs G, Kopper L, Sebestyen A. 2015. Expression of Certain Leukemia/Lymphoma Related microRNAs and its Correlation with Prognosis in Childhood Acute Lymphoblastic Leukemia. Pathol Oncol Res 21(3):597-604.

Nishioka C, Ikezoe T, Yang J, Nobumoto A, Tsuda M, Yokoyama A. 2014. Downregulation of miR-217 correlates with resistance of ph(+) leukemia cells to ABL tyrosine kinase inhibitors. Cancer Sci 105(3):297-307.

O'Connell RM, Kahn D, Gibson WSJ, Round JL, Scholz RL, Chaudhuri AA, Kahn ME, Rao DS, Baltimore D. 2010. MicroRNA-155 Promotes Autoimmune Inflammation by Enhancing Inflammatory T Cell Development. Immunity 33(4):607-619.

Ohyashiki J, Umezu T, Kurada M, Ohyashiki K. 2010. Dysregulation of Mir-92a, as a Possible Apoptosis Inhibitor, Indicates Poor Prognosis in Acute Lymphoblastic Leukemia. Haematol-Hematol J 95:87-88.

Olive V, Bennett MJ, Walker JC, Ma C, Jiang I, Cordon-Cardo C, Li QJ, Lowe SW, Hannon GJ, He L. 2009. miR-19 is a key oncogenic component of mir-17-92. Genes & development 23(24):2839-2849.

Organista-Nava J, Gomez-Gomez Y, Illades-Aguiar B, Alarcon-Romero LD, Saavedra-Herrera MV, Rivera-Ramirez AB, Garzon-Barrientos VH, Leyva-Vazquez MA. 2015. High miR-24 expression is associated with risk of relapse and poor survival in acute leukemia. Oncol Rep 33(4):1639-1649.

Ortega M, Bhatnagar H, Lin AP, Wang L, Aster JC, Sill H, Aguiar RCT. 2015. A microRNA-mediated regulatory loop modulates NOTCH and MYC oncogenic signals in B- and T-cell malignancies. Leukemia 29(4):968-976.

Ottmann OG, Wassmann B, Pfeifer H, Giagounidis A, Stelljes M, Duhrsen U, Schmalzing M, Wunderle L, Binckebanck A, Hoelzer D. 2007. Imatinib compared with chemotherapy as front-line treatment of elderly patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph plus ALL). Cancer 109(10):2068-2076.

Pica A, Di Santi A, D'angelo V, Iannotta A, Ramaglia M, Di Martino M, Pollio ML, Schiattarella A, Borrelli A, Mancini A, Indolfi P, Casale F. 2015. Effect of rMnSOD on Survival Signaling in Pediatric High Risk T-Cell Acute Lymphoblastic Leukaemia. Journal of cellular physiology 230(5):1086-1093.

825 Prakash G, Kaur A, Malhotra P, Khadwal A, Sharma P, Suri V, Varma N, Varma S. 2016. Current
826 Role of Genetics in Hematologic Malignancies. Indian J Hematol Blo 32(1):18-31.
827 Raji GR, Sruthi TV, Edatt L, Haritha K, Shankar SS, Kumar VBS. 2017. Horizontal transfer of
828 miR-106a/b from cisplatin resistant hepatocarcinoma cells can alter the sensitivity of
829 cervical cancer cells to cisplatin. Cellular signalling 38:146-158.
830 Rao R, Nagarkatti PS, Nagarkatti M. 2015. Delta(9)Tetrahydrocannabinol attenuates
831 Staphylococcal enterotoxin B-induced inflammatory lung injury and prevents mortality in
832 mice by modulation of miR-17-92 cluster and induction of T-regulatory cells. Brit J
833 Pharmacol 172(7):1792-1806.
834 Re A, Cora D, Taverna D, Caselle M. 2009. Genome-wide survey of microRNA-transcription factor
835 feed-forward regulatory circuits in human. Mol Biosyst 5(8):854-867.
836 Sattler M, Scheijen B, Weisberg E, Griffin JD. 2003. Mutated tyrosine kinases as therapeutic targets
837 in myeloid leukemias. Adv Exp Med Biol 532:121-140.
838 Schotte D, De Menezes RX, Akbari MF, Khankahdani LM, Lange-Turenhout E, Chen C, Pieters R,
839 Den Boer ML. 2011. MicroRNAs characterize genetic diversity and drug resistance in
840 pediatric acute lymphoblastic leukemia (vol 96, pg 703, 2011). Haematol-Hematol J
841 96(8):1240-1240.
842 Schotte D, de Menezes RX, Moqadam FA, Lange-Turenhout E, Chen CF, Pieters R, Den Boer ML.
843 2009. MicroRNAs Characterize Genetic Diversity and Drug Sensitivity in Pediatric Acute
844 Lymphoblastic Leukemia. Blood 114(22):41-41.
845 Seddiki N, Brezar V, Ruffin N, Levy Y, Swaminathan S. 2014. Role of miR-155 in the regulation
846 of lymphocyte immune function and disease. Immunology 142(1):32-38.
847 Slavov SN, Teixeira HLG, Rego EM. 2010. The role of micro-ribonucleic acids in normal
848 hematopoiesis and leukemic T-lymphogenesis. Braz J Med Biol Res 43(7):619-626.
849 Somasundaram R, Prasad MAJ, Ungerback J, Sigvardsson M. 2015. Transcription factor networks
850 in B-cell differentiation link development to acute lymphoid leukemia. Blood 126(2):144-
851 152.
852 Speck NA, Gilliland DG. 2002. Core-binding factors in haematopoiesis and leukaemia. Nature
853 Reviews Cancer 2(7):502-513.
854 Tanaka M, Oikawa K, Takanashi M, Kudo M, Ohyashiki J, Ohyashiki K, Kuroda M. 2009. Down-
855 Regulation of miR-92 in Human Plasma Is a Novel Marker for Acute Leukemia Patients.
856 PloS one 4(5).
857 Tasian SK, Doral MY, Borowitz MJ, Wood BL, Chen IM, Harvey RC, Gastier-Foster JM, Willman
858 CL, Hunger SP, Mullighan CG, Loh ML. 2012. Aberrant STAT5 and PI3K/mTOR pathway
859 signaling occurs in human CRLF2-rearranged B-precursor acute lymphoblastic leukemia.
860 Blood 120(4):833-842.
861 Thai TH, Calado DP, Casola S, Ansel KM, Xiao CC, Xue YZ, Murphy A, Frendewey D,
862 Valenzuela D, Kutok JL, Schmidt-Supprian M, Rajewsky N, Yancopoulos G, Rao A,
863 Rajewsky K. 2007. Regulation of the germinal center response by microRNA-155. Science
864 316(5824):604-608.
865 Thomas MD, Kremer CS, Ravichandran KS, Rajewsky K, Bender TP. 2005. c-Myb is critical for B
866 cell development and maintenance of follicular B cells. Immunity 23(3):275-286.
867 Tsang J, Zhu J, van Oudenaarden A. 2007. MicroRNA-mediated feedback and feedforward loops
868 are recurrent network motifs in mammals. Molecular cell 26(5):753-767.
869 Tye CE, Gordon JAR, Martin-Buley LA, Stein JL, Lian JB, Stein GS. 2015. Could lncRNAs be the
870 Missing Links in Control of Mesenchymal Stem Cell Differentiation? Journal of cellular
871 physiology 230(3):526-534.
872 Van Peer G, Lefever S, Anckaert J, Beckers A, Rihani A, Van Goethem A, Volders PJ, Zeka F,
873 Ongenaert M, Mestdagh P, Vandesompele J. 2014. miRBase Tracker: keeping track of
874 microRNA annotation changes. Database-Oxford.

Verduci L, Azzalin G, Gioiosa S, Carissimi C, Laudadio I, Fulci V, Macino G. 2015. microRNA-181a enhances cell proliferation in acute lymphoblastic leukemia by targeting EGR1. Leukemia research 39(4):479-485.

Vignetti M, Fazi P, Cimino G, Martinelli G, Di Raimondo F, Ferrara F, Meloni G, Ambrosetti A, Quarta G, Pagano L, Rege-Cambrin G, Elia L, Bertieri R, Annino L, Foa R, Baccarani M, Mandelli F. 2007. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. Blood 109(9):3676-3678.

Vilimas T, Mascarenhas J, Palomero T, Mandal M, Buonamici S, Meng FY, Thompson B, Spaulding C, Macaroun S, Alegre ML, Kee BL, Ferrando A, Miele L, Aifantis I. 2007. Targeting the NF-kappa B signaling pathway in Notch1-induced T-cell leukemia. Nature medicine 13(1):70-77.

Wang J, Chen JY, Sen S. 2016. MicroRNA as Biomarkers and Diagnostics. Journal of cellular physiology 231(1):25-30.

Weilner S, Grillari-Voglauer R, Redl H, Grillari J, Nau T. 2015. The role of microRNAs in cellular senescence and age-related conditions of cartilage and bone. Acta Orthop 86(1):92-99.

Weiner LM, Surana R, Wang SZ. 2010. Monoclonal antibodies: versatile platforms for cancer immunotherapy. Nat Rev Immunol 10(5):317-327.

Weng AP, Millholland JM, Yashiro-Ohtani Y, Arcangeli ML, Lau A, Wai C, Bianco C, Rodriguez CG, Sai H, Tobias J, Li Y, Wolfe MS, Shachaf C, Felsher D, Blacklow SC, Pear WS, Aster JC. 2006. c-Myc is an important direct target of Notch1 in T-cell acute lymphoblastic leukemia/lymphoma. Genes & development 20(15):2096-2109.

Wong J, Welschinger R, Hewson J, Bradstock KF, Bendall LJ. 2014. Efficacy of dual PI-3K and mTOR inhibitors in Vitro and in Vivo in acute lymphoblastic leukemia. Oncotarget 5(21):10460-10472.

Xiao CC, Calado DP, Galler G, Thai TH, Patterson HC, Wang J, Rajewsky N, Bender TP, Rajewsky K. 2007. MiR-150 controls B cell differentiation by targeting the transcription factor c-myb. Cell 131(1):146-159.

Xiao CC, Srinivasan L, Calado DP, Patterson HC, Zhang BC, Wang J, Henderson JM, Kutok JL, Rajewsky K. 2008. Lymphoproliferative disease and autoimmunity in mice with increased miR-17-92 expression in lymphocytes. Nat Immunol 9(4):405-414.

Xiao GF, Tang HH, Wei W, Li J, Ji LD, Ge J. 2014. Aberrant Expression of MicroRNA-15a and MicroRNA-16 Synergistically Associates with Tumor Progression and Prognosis in Patients with Colorectal Cancer. Gastroent Res Pract.

Xu JA, Li CX, Li YS, Lv JY, Ma Y, Shao TT, Xu LD, Wang YY, Du L, Zhang YP, Jiang W, Li CQ, Xiao Y, Li X. 2011. MiRNA-miRNA synergistic network: construction via co-regulating functional modules and disease miRNA topological features. Nucleic Acids Res 39(3):825-836.

Yang Z, Wan XS, Gu ZY, Zhang HH, Yang XB, He L, Miao RY, Zhong Y, Zhao HT. 2014. Evolution of the mir-181 microRNA family. Comput Biol Med 52:82-87.

Ye HS, Liu XW, Lv M, Wu YL, Kuang SZ, Gong J, Yuan P, Zhong ZD, Li QB, Jia HB, Sun J, Chen ZC, Guo AY. 2012. MicroRNA and transcription factor co-regulatory network analysis reveals miR-19 inhibits CYLD in T-cell acute lymphoblastic leukemia. Nucleic Acids Res 40(12):5201-5214.

Zaidi SK, Perez AW, White ES, Lian JB, Stein JL, Stein GS. 2017. An AML1-ETO/miR-29b-1 regulatory circuit modulates phenotypic properties of acute myeloid leukemia cells. Oncotarget 8(25):39994-40005.

Zare-Maivan H, Khanpour-Ardestani N, Ghanati F. 2017. Influence of mycorrhizal fungi on growth, chlorophyll content, and potassium and magnesium uptake in maize. J Plant Nutr 40(14):2026-2032.

926 Zhang H, Chen YQ. 2009. New insight into the role of miRNAs in leukemia. Sci China Ser C
927 52(3):224-231.
928 Zhang H, Li Y, Lai M. 2010. The microRNA network and tumor metastasis. Oncogene 29(7):937-
929 948.
930 Zhang H, Luo XQ, Zhang P, Huang LB, Zheng YS, Wu J, Zhou H, Qu LH, Xu L, Chen YQ. 2009.
931 MicroRNA Patterns Associated with Clinical Prognostic Parameters and CNS Relapse
932 Prediction in Pediatric Acute Leukemia. PloS one 4(11).
933 Zhang LS, Zhou Y, Chen K, Shi PC, Li Y, Deng MM, Jiang ZW, Wang XM, Li P, Xu B. 2017. The
934 pan-Bcl2 Inhibitor AT101 Activates the Intrinsic Apoptotic Pathway and Causes DNA
935 Damage in Acute Myeloid Leukemia Stem-Like Cells. Targeted oncology 12(5):677-687.
936 Zhao G, Wang B, Liu Y, Zhang JG, Deng SC, Qin Q, Tian K, Li X, Zhu S, Niu Y, Gong Q, Wang
937 CY. 2013. miRNA-141, Downregulated in Pancreatic Cancer, Inhibits Cell Proliferation and
938 Invasion by Directly Targeting MAP4K4. Molecular cancer therapeutics 12(11):2569-2580.
939 Zheng LL, Tu QS, Meng S, Zhang L, Yu LM, Song JL, Hu Y, Sui L, Zhang J, Dard M, Cheng J,
940 Murray D, Tang Y, Lian JB, Stein GS, Chen J. 2017. Runx2/DICER/miRNA Pathway in
941 Regulating Osteogenesis. Journal of cellular physiology 232(1):182-191.

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