MicroRNA-486-5p is an erythroid oncomiR of the myeloid leukemias of Down syndrome

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Key Points
- miR-486-5p, a GATA1 regulated miR, is expressed in ML-DS and enhances their aberrant erythroid phenotype.
- miR-486-5p cooperates with GATA1s to promote the survival of pre-leukemic and leukemic cells.

Children with Down syndrome (DS) are at increased risk for acute myeloid leukemias (ML-DS) characterized by mixed megakaryocytic and erythroid phenotype and by acquired mutations in the GATA1 gene resulting in a short GATA1s isoform. The chromosome 21 microRNA (miR)-125b cluster has been previously shown to cooperate with GATA1s in transformation of fetal hematopoietic progenitors. In this study, we report that the expression of miR-486-5p is increased in ML-DS compared with non-DS acute megakaryocytic leukemias (AMKLs). miR-486-5p is regulated by GATA1 and GATA1s that bind to the promoter of its host gene ANK1. miR-486-5p is highly expressed in mouse erythroid precursors and knockdown (KD) in ML-DS cells reduced their erythroid phenotype. Ectopic expression and KD of miR-486-5p in primary fetal liver hematopoietic progenitors demonstrated that miR-486-5p cooperates with GATA1s to enhance their self renewal. Consistent with its activation of AKT, overexpression and KD experiments showed its importance for growth and survival of human leukemic cells. Thus, miR-486-5p cooperates with GATA1s in supporting the growth and survival, and the aberrant erythroid phenotype of the megakaryocytic leukemias of DS. (Blood. 2015;125(8):1292-1301)

Introduction

Children with Down syndrome (DS) have a markedly increased risk for a subtype of myeloid leukemia (ML) classified by the World Health Organization as ML-DS.1 These acute megakaryocytic leukemias (AMKLs) often co-express erythroid genes and surface proteins2-4 and have unique clinical and genetic features.5-8 They evolve in two distinct clinical stages; up to 10% of affected children are born with a transient myeloid proliferative disorder and in a fifth of these patients, full blown ML-DS is diagnosed by the age of 4 years.7,9,10 Both the congenital transient leukemia and the established ML-DS are characterized by somatic in utero mutations in the X-chromosome gene GATA1, which arise during fetal liver (FL) hematopoiesis.11-14 GATA1 encodes a transcription factor that regulates the development and maturation of the megakaryocytic-erythroid lineages (lins).15 Strikingly, all GATA1 mutations in ML-DS result in the expression of a shorter isoform GATA1s, which lacks the amino terminal “transactivation domain.”12 These mutations have both loss- and gain-of-function consequences. Although GATA1s is less active than GATA1 in promoting megakaryocytic differentiation, it enhances proliferation of fetal megakaryocytic progenitors.12,16 Klusmann et al suggested that the enhancing effect on proliferation is caused by cooperation between GATA1s and insulin growth factor-P13K-AKT-mTOR signaling during FL hematopoiesis.17

MicroRNAs (miRs) have multiple roles in regulating growth and differentiation of normal and leukemic hematopoietic cells.18-20 It has been previously demonstrated that miR-125b-2, encoded by a gene on chromosome 21, is overexpressed in ML-DS and cooperates with GATA1s in the transformation of FL hematopoietic progenitors.21 Here, we describe the expression and function of miR-486-5p in ML-DS. miR-486-5p is a muscle-enriched miR whose loss has been suggested to be involved in muscular dystrophy.22-26 While conflicting data were published regarding a tumor suppressive or oncogenic roles in several solid tumors,27,28 it has never been reported in hematologic malignancies. In this study, we show that miR-486-5p expression in ML-DS is enhanced by GATA1s, and promotes the survival and the unique erythroid phenotype of these megakaryoblastic leukemias.
Materials and methods

Cell lines

Human embryonic kidney 293T cells were grown in Dulbecco’s modified Eagle medium (GIBCO) supplemented with 10% fetal bovine serum (FBS) (GIBCO), 1% glutamine (GIBCO), penicillin (100 U/mL), and streptomycin (100 μg/mL). Human leukemia cell lines, CMK, CMY, CMS, and K562 were grown in RPMI (GIBCO) supplemented with 10% FBS, 1% glutamine, 1% penicillin/streptomycin (GIBCO), and 10 ng/mL thrombopoietin (TPO) (PeproTech). Following transduction, cells were cultured in differentiation medium containing 10 ng/mL TPO (PeproTech), 2 μM erythropoietin (EPO) (Amgen), and 50 ng/mL stem cell factor (SCF) (PeproTech).

Patient samples

RNA from diagnostic or remission bone marrow (BM) samples of DS-AMKL and non-DS-AMKL patients were obtained following informed consent from patients enrolled in the Children’s Oncology Group AAML0431 clinical trial “The Treatment of Down Syndrome Children With Acute Myeloid Leukemia and Myelodysplastic syndrome Under the Age of 4 Years” and from the Children’s Hospital of Michigan Leukemia Cell Bank. The samples were anonymized before shipping except for the information on the genetic subgroup. The study was approved by the institutional review boards of the Israeli Health Ministry, Sheba Medical Center, and Wayne State University according to the requirements of the Declaration of Helsinki. The FL studies were conducted according to the Declaration of Helsinki principles, under a protocol approved by the institutional review board at The Children’s Hospital of Philadelphia.

miR arrays

Custom miR microarrays were prepared by Rosetta Genomics Ltd as described previously. Briefly, DNA oligonucleotide probes were spotted in triplicate on coated microarray slides. About 3 to 5 μg of total RNA were labeled by ligation of an RNA-linker, p-3Ct-Cy3/dye to the 3’ end. Slides were incubated with the labeled RNA and washed twice. Arrays were scanned at a resolution of 10 μm, and images were analyzed using SpotReader software (Niles Scientific, Portola Valley, CA). Microarray spots were combined and signals normalized to the expression of all the measured miRs as described previously. Significance of differences was assessed by a two-sided unpaired t test. Fold-change was calculated as the ratio of the median values of the normalized fluorescence signals in the 2 groups.

TaQMan miR assay

Total RNA, including miR, was extracted from cells using cold TRIzol (Invitrogen, Carlsbad CA). miR-125b-5p, miR-99a, miR-486-5p, miR-486-3p, RNU19, and RNU43-specific complementary DNAs were transcribed and amplified using gene-specific primer sets following the TaQMan miR assay protocol (Applied Biosystems, Foster City, CA). RNU19 or RNU43 were used as human internal controls, and snoRNA142 or snoRNA 202 were used as mouse internal controls. Samples were tested in duplicate on the Applied Biosystems 7900HT Fast Real-Time PCR System.

Real time quantitative reverse-transcription polymerase chain reaction (qRT-PCR)

qRT-PCR assays were developed to determine the level of messenger RNA (mRNA) expression of different genes using SYBR Green (Applied Biosystems, Warrington, United Kingdom). Forward and reverse primers (Sigma-Aldrich, St. Louis, MO) were designed from different exons in order to eliminate DNA contamination (see supplemental Table 1 on the Blood Web site). Actin was used as endogenous control. Human GATA1 and human pri-miR-486 expression were examined using TaQMan gene expression assay and RPLPO was used as endogenous control (Applied Biosystems). Samples were tested in duplicate on the Applied Biosystems 7900HT Fast Real-Time PCR System.

Retrovirus vectors

The MSCV-PIG retroviral vector was used to generate expression vectors for miR-486-5p, miR-125b, and miR-mutant-125b as previously described. Replication incompetent retroviruses were obtained by transient transfection of 293T cells with retroplasmids, together with pCGP and pMD2G for transducing the human leukemia cell line CMS, or pCMV-Eco for transducing FL mouse cells. Transduced cells were selected using 2 μg/mL puromycin or identified by green fluorescent protein expression.

Lentiviral vector expressing short hairpin RNA (shRNA) anti-miR-486-5p and miR-486-5p were kindly provided by Dr Ravi Bhatia (City of Hope National Medical Center, Duarte, CA). Replication incompetent retroviruses were obtained by transient transfection of 293T cells with retroplasmids, together with pSVG, pREV, and pMDL.

MIGR1 retroviral vector expressing murine Gata1 or Gata1s were kindly provided by Dr J. Crispino (Northwestern University, Chicago, IL). PLKO.1 retroviral vector expressing shRNA anti-human GATA1 (all isoforms) and control vector were purchased from Sigma-Aldrich.

Western blotting

Protein extracts were prepared by resuspending cells in radioimmunoprecipitation assay lysis buffer containing 1% NP40, 0.5% Na-Deoxycholate, 0.1% sodium dodecyl sulfate, and protease inhibitors (Roche). Proteins were resolved on 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis gels and transferred to nitrocellulose membranes. Membranes were blocked with 5% nonfat milk in phosphate-buffered saline (PBS) and 0.1% Tween-20, and labeled with primary antibodies anti-β-Actin (#3700; Cell Signaling, Danvers, MA), total AKT (Cell Signaling), anti-P-AKT (Ser 473; Cell Signaling), and followed by incubation with a secondary, peroxidase-conjugated antibody (Jackson ImmunoResearch Laboratories; #115-035-146 and #115-035-144, diluted 1:10000). Peroxidase activity was detected by exposing the membrane with chemiluminescence solution containing 150 mM Tris (pH 8.9), 0.22 mg/mL luminol (Sigma-Aldrich), 0.033 mg/mL paracoumaric acid (Sigma-Aldrich), and 0.015% H2O2.

Chromatin immunoprecipitation sequencing was performed as recently described.

Mega[karyocytic differentiation and miR profiling of human FL

Human FL mononuclear cells were cultured in serum-free medium (StemSpan SFEM, Stemcell Technologies, Vancouver, Canada) supplemented with 100 ng/mL TPO (R&D Systems, Minneapolis, MN), 40 μg/mL low density lipoprotein (Calbiochem, San Diego, CA) and 1% penicillin/streptomycin (Gibco Invitrogen, Carlsbad, CA). RNA was isolated from megakaryocytes on day 10 of differentiation with the RNeasy Kit (Qiagen) and hybridized to Affymetrix HuGene 1.0 ST arrays.

Sorting of mouse hematopoietic cells

BM cells were isolated from the femurs of 4-month-old C57BL/6 wild-type (WT) and GATA1s KI mice. Single-cell suspensions were washed in PBS with 0.05M EDTA and 0.1% bovine serum albumin. The lin− progenitors were isolated using the Lineage Cell Depletion Kit (Miltenyi Biotec). Megakaryocyte-erythroid progenitors (MEPs) (Sca1−, c-Kit+, Flk2+, and CD34+) were sorted from the Lin− population after staining with phycoerythrin (PE)-Cy7–conjugated anti–C-kit, fluorescein isothiocyanate–conjugated anti-Sca1, APC–conjugated FcγR, and PE–conjugated CD34 (eBioscience) using the BD FACS/Aria sorter (BD Biosciences). Erythroid cells (Ter 119+) were sorted from the Lin− population after staining with fluorescein isothiocyanate–conjugated Ter119 (eBioscience), and megakaryocytic cells (CD41+) were sorted from the Lin− population after staining with PE–conjugated CD41 (eBioscience) using the BD FACS/Aria sorter (BD Biosciences).
Flow cytometric analysis

Cells were washed in PBS, stained with 7-AAD for the exclusion of nonviable cells, and stained with PE-conjugated CD235a (BioLegend), APC-conjugated CD61 (BioLegend), and APC-conjugated Annexin V (BD Pharmigen) according to the intended analysis. Analysis was performed on the Gallios flow cytometer and data were elaborated using Kaluza software (Coulter).

Proliferation assay

Proliferation was evaluated by MTT assay (Sigma-Aldrich) according to manufacturer’s instructions.

Analysis of G1ME cells

MIGR1 retroviral vectors expressing GATA1 or GATA1s were generated as described.40 G1ME cells were collected 72 hours after transduction. Ter119 cells were isolated by 1 of 2 methods: 1) the cells were stained with a Ter119-APC antibody (BD Pharmingen) and separated on a FACSAria II cell sorter (BD Biosciences), or 2) they were stained with a Ter119-biotin antibody (BD Pharmingen) and isolated with EasySep RapidSpheres (Stemcell Technologies).

Methylcellulose cultures of transduced mouse FL cells

FL cells E12.5 were extracted from Gata1s knock-in (KI) or WT C57BL/6 mice. The cells were sorted for Ter119+ cells using anti–Ter-119 magnetic MicroBeads (Miltenyi Biotec). Some 2 × 105 Ter119+ FL cells were transduced in 2 cycles of transduction with the following: miR-125b, mutant miR-125b, miR-486, or empty vector, together with 5 ug/mL polybrene. The next day, 1.5 × 104 were seeded in MethoCult M3231 methylcellulose medium (Stemcell Technologies) supplied with 50 ng/mL murine TPO and 100 ng/mL murine SCF (PeproTech) in a 3-cm well plate. Approximately each week, the colonies were counted and replated (1.5 × 104 cells) in the same condition. Four cycles of replating were performed.

Statistics

Data obtained from multiple experiments were reported as the mean ± SEM. Significance levels were determined by Student’s t test and analysis of variance...
Results

To identify miRs that are differentially expressed in ML-DS, we used micro-arrays to interrogate RNA derived from 20 diagnostic BM of patients with ML-DS, 6 with ML-DS in remission, and 3 with non-DS (NDS) AMKL. Four miRs, miR-99a, -100, -125b-2, and -486-5p, whose expression was highest in ML-DS (Figure 1A), were further validated by qRT-PCR in 55 independent BM samples (36 ML-DS at diagnosis, 7 ML-DS in remission, and 12 NDS-AMKL at diagnosis) (Figure 1B). miR-125b-2 and miR-99a are encoded by genes on chromosome 21, and were previously reported to be highly expressed and to have a leukemogenic role in ML-DS. miR-100 is a homolog of miR-99a. We decided, therefore, to further investigate miR-486 since it has never been reported to be associated with hematologic malignancies. We focused on the main isoform miR-486-5p, whose expression was higher than the miR-486-3p (supplemental Figure 1). We herein use the terminology “miR-486” to refer to both isoforms, and “miR-486-5p” or “miR-486-3p” for the specific isoforms.

Regulation of miR-486-5p expression in ML-DS

miR-486 is located in the last intron of ANK1, which encodes ankyrin-1, the prototype member of a family of proteins linking integral membrane proteins to the underlying spectrin-actin cytoskeleton. ANK1 was
first discovered in erythrocytes and is mutated in hereditary spherocytosis, and is a known target of GATA1. Similar to the expression of miR-486, the expression of ANKI mRNA is higher in BM cells of patients with ML-DS compared with non-DS AMKL (supplemental Figure 2A). Furthermore, GATA1 and GATA1s bind to the same site in the 5' end of the erythroid isoform of ANKI, a site whose epigenetic analysis is consistent with an active promoter region (supplemental Figure 2B-C). Because miRs are often transcribed with their host genes, we hypothesized that GATA1 and GATA1s may regulate miR-486 expression.

GATA1s is a short isoform of GATA1 that lacks the amino terminal domain. GATA1s is normally co-expressed with the full length GATA1 in MEPs, whereas only GATA1s is expressed in ML-DS. GATA1s was previously reported to be more highly expressed in ML-DS compared with non-DS AMKL. We confirmed the increased level of GATA1s mRNA in ML-DS (n = 36) compared with the levels of both isoforms of GATA1 in NDS-AMKL (n = 12) and in remission BM (n = 7) (Figure 2A, P = .009, ANOVA). We then observed that the level of miR-486-5p in DS diagnostic leukemia samples was highly correlated with the level of GATA1s expression (Figure 2B, R = .793, P < .01 ANOVA), suggesting that it may be regulated by GATA1s. Consistent with this hypothesis, the expression of miR-486-5p was reduced after shRNA-mediated knockdown (KD) of GATA1s in ML-DS CMK and CMY cells (Figure 2C). Conversely, ectopic expression of GATA1s or GATA1 full-length isoform (herein referred as “GATA1”) in the erythroid leukemia K562 cells enhanced the expression of miR-486-5p (Figure 2E). The magnitude of levels of miR-486-5p expression correlated with the magnitude of change in GATA1s or GATA1 in the 3 experiments (Figure 2F-H, compare panels C-E to F-H). Similar results were observed with miR-486-3p and with the primary transcript pri-miR-486 (supplemental Figure 3), indicating that GATA1s regulates the transcription of miR-486. Together, these results suggest that the increased expression of miR-486 in DS-AMKL is at least partially caused by the increased expression of GATA1s.

miR-486 is an erythropoietic miR

To further explore the regulation of miR-486 by GATA1s, we analyzed its expression in sorted hematopoietic cells from BM of wt and Gata1s KI male C57BL/6 mice. In both genotypes, the miR-486-5p was expressed in lin− and MEPs, and was dramatically increased in erythroid Ter119+ cells (Figure 3A, P < .01). Its expression in sorted CD41− Ter119+ megakaryocytic cells was barely detectable (data not shown). Within erythroid cells, its expression was higher in Gata1s KI correlating with the higher Gata1s mRNA levels (compare Figure 3Ai to Figure 3Aii).

To test more directly whether Gata1 regulates the expression of miR-486, we expressed either Gata1 or Gata1s by retroviral transduction into Gata1, and to a lesser degree, Gata1s expression. The expression of Gata1, and to a lesser degree, Gata1s expression. The expression of Gata1, and to a lesser degree, Gata1s expression.
of its regulation by the Gata1 and Gata1s isoforms may depend on the specific cellular/developmental contexts.

Consistent with the pattern of expression in mouse hematopoietic cells, GYPA mRNA, encoding the erythroid membrane protein glycophorin A, was 3 times higher in ML-DS compared with NDS-AMKL as determined by published micro-array analysis3 (Figure 4A). In our 36 diagnostic BM samples of ML-DS quantified by qRT-PCR, GYPA mRNA correlated significantly with the levels of miR-486-5p (Figure 4B) (R = 0.751, P < .01) (2-tailed Student t test). SCR, scrambled.

**Figure 4. miR-486 is important for the ML-DS erythroid phenotype.** (A) GYPA (glycophorin A and CD235) expression in diagnostic BM of ML-DS patients (n = 25) compared with non–DS-AMKL (n = 38), published microarray data.3 (B) Pearson correlation test between the expression level of GYPA and miR-486-5p determined by qRT-PCR in diagnostic BM of 36 ML-DS patients. **Correlation was statistically significant, P < .01 (ANOVA). (C) Expression of miR-486-5p in CMK and CMY ML-DS cells stably expressing shRNA anti–miR-486-5p (miR-486-5p-KD) or SCR. (D) GYPA and CD61 expression in CMK ML-DS cells stably expressing shRNA anti–miR-486-5p or SCR determined by flow cytometry. (E) Increase of cells with pure megakaryocytic phenotype (GYPA+ and CD61+) in CMK and CMY ML-DS cells stably expressing shRNA anti–miR-486-5p in comparison with SCR. *P < .01 (2-tailed Student t test). SCR, scrambled.

Pro-leukemogenic roles of miR-486-5p

In myogenic cells miR-486 has been previously reported to activate PI3K/AKT through enhanced phosphorylation caused by targeting inhibitory phosphatases.22,24,25 We observed the same in leukemic cells by KD and overexpression (OE) of miR-486-5p in ML-DS and NDS-AMKL cells, respectively (Figure 5A,B). We (Y. Ge and J.W.T.) previously reported that ML-DS cells are highly sensitive to PI3K inhibitors.49 Accordingly, KD of miR-486 reduced the
miR-125b (positive control21), miR-125b mutated in its seed nucleotides (negative control17), or empty vector, and plated in methylcellulose cultures supplemented with TPO (50 ng/mL) and SCF (100 ng/mL). Colonies were counted and replated every week. Unlike miR-125b, a known myeloid oncogene,18 cells transduced with miR-486-5p did not form colonies beyond the first culture (Figure 6A).

The GATA1s isoform has been shown to enhance the proliferation and self-renewal of myeloid progenitors.16,17,48,50 Therefore, we next asked whether miR-486-5p can enhance the oncogenic effects of GATA1s similar to what was shown for miR-125b.21 E12.5 Gata1s KI FL hematopoietic progenitors were transduced with the same vectors and replating assays were performed for 4 cycles (Figure 6B). As was previously reported,21 the presence of Gata1s alone enabled self-renewal that was markedly enhanced by miR-125b as measured by the numbers of colonies in each cycle of replating. miR-486-5p also enhanced replating efficiency, although to a lesser degree than miR-125b (P < .05, 2-tailed Student t test).

Because miR-486 is already expressed in Gata1s hematopoietic progenitors (Figure 3A), we next asked if this endogenous expression contributes to the self-renewal capacity endowed by Gata1s. Thus, we transduced primary E12.5 FL Gata1s KI hematopoietic progenitors with shRNA against miR-486-5p, achieving 90% KD (Figure 6C) and observed progressively reduced numbers of colonies in each replating (Figure 6D, P < .05, 2-tailed Student t test).

Collectively, our data suggest that the GATA1s in DS-AMKL enhances the expression of miR-486, which then collaborates with GATA1s in enhancing self-renewal of FL hematopoietic progenitors.

Discussion

The MLs of DS are unique in the expression of somatically mutated GATA1, preserving the GATA1s isoform, and the co-expression of megakaryocytic and erythroid markers on the surface of the same cells. There is no normal counterpart to such cells as the bi-potential MEPs express neither megakaryocytic nor erythroid differentiation antigens. Here, we report that miR-486-5p enhances the survival and the erythroid immunophenotype of ML-DS leukemic cells.

The first question we asked is why miR-486 is specifically expressed in ML-DS. Our experiments strongly suggest that miR-486 expression is regulated by both GATA1 and GATA1s in a dose-dependent manner. KD of GATA1s reduced miR-486 expression in ML-DS, whereas its OE in the erythroid leukemia cells increased miR-486 expression. Erythroid progenitors from Gata1s KI mice also displayed increased expression of miR-486 compared with the same lin cells from wt BM correlating with higher Gata1s mRNA levels. Because we confirmed the previous report3 that the levels of GATA1s expression in ML-DS are 3 to 4 times higher than NDS-AMKL, it seems reasonable to conclude that the higher level of expression of miR-486 in ML-DS is caused by the increased expression of GATA1s.

Yet, in contrast to the observations in human leukemia cells and in primary mouse erythroid cells, the expression of Gata1s in the Gata1 null G1ME cell line resulted in a smaller induction of miR-486-5p expression compared with the Gata1 isoform. These data suggest that the effect of Gata1s on the expression of miR-486 may depend on the specific cellular and developmental context, and on the interaction with other co-factors as recently shown by Chlon et al.38

Both trisomy 21 and GATA1s cooperate in an expansion of human fetal MEPs,51-53 which probably explains why these leukemias are always diagnosed in early childhood.8 We did not detect any significant differences in miR-486 expression in pure megakaryocytic cultures...
miR-486 is encoded within ANK1, a GATA1-regulated gene highly expressed in erythroid precursor cells. ANKI expression is increased in ML-DS and its expression changed in the same direction with miR-486 in all the experiments reported in this study (data not shown). Yet, this could reflect the changes in the erythroid phenotype and is not direct evidence for co-transcription. The regulation of miR within host genes is complex. Complicating the matter is that miR-486 may be transcribed from both DNA strands. Hence, further research is required to uncover additional regulatory factors of miR-486 in erythroid cells.

Although cloned from the human FL, there is only one report on the involvement of miR-486 in hematopoiesis. Lulli et al recently reported that miR-486-3p regulates fetal hemoglobin by suppression of BCL11A in fetal erythroid cells, although it did not affect their growth and survival. We show here that miR-486-5p is not merely a marker of erythroid progenitors, but rather a regulator of the erythroid phenotype of ML-DS leukemic cells. Our results are supported by independent observations of Bhatia et al., in which ectopic miR-486-5p expression enhanced in vitro erythroid differentiation of normal CD34+ cells. Interestingly, miR-486-5p activates AKT (Figure 5A,B), which has been previously shown to be important for erythroid differentiation. Additional studies will be needed to clarify the roles of miR-486 in normal erythropoiesis, and possibly, in regulating the decision between megakaryocytic and erythroid differentiation.

We further demonstrate that miR-486-5p cooperates with Gata1s in enhancing colony number and self-renewal of FL hematopoietic progenitors and that it is important for the survival of ML-DS cells. Previous research demonstrated the dependency of ML-DS on PI3K-AKT signaling. For example, Klusmann et al showed that the loss of the amino-terminal domain in the Gata1s isoform relieves repression of E2F1 and induces proliferation of fetal mega-erythroid progenitors. They showed that insulin growth factor 1-PI3K-AKT signaling pathway cooperates with activated E2F1 in these cells and hypothesized that trisomy 21 had a role in the activation of that pathway. We speculate that miR-486-5p provides this “missing link,” as it is a strong activator of AKT in ML-DS. The similar observations in chronic ML by Bhatia et al suggest that miR-486-5p may be an important oncogene in several hematopoietic myeloid malignancies characterized by dependency on the PI3K/AKT pathway.

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References


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