

# Targeting Protein Arginine Methyltransferase 1 Blocks RBM15-MKL1 Fusion-Initiated Human Stem Cell Transformation

Jin S<sup>1,2</sup>, Yao Z<sup>3</sup>, Mi Y<sup>3</sup>, Wang H<sup>2</sup>, Yao S<sup>2</sup>, Song J<sup>1</sup>, Zhang P<sup>3</sup>, Zhang J<sup>2</sup>, Zhou W<sup>2</sup>, Ma J<sup>4</sup>, Guo Y<sup>4</sup> and Liu Y<sup>2\*</sup>

<sup>1</sup>Department of Internal Medicine, the Second Affiliated Hospital of Zhengzhou University, Zhengzhou, China

<sup>2</sup>Department of Internal Medicine, Henan Cancer Hospital and Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China

<sup>3</sup>Department of Otolaryngology and Head Neck Surgery, the Second Affiliated Hospital of Zhengzhou University, Zhengzhou, China

<sup>4</sup>Department of Molecular Pathology, Henan Cancer Hospital and Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China

## Abstract

**Objective:** The chromosome translocation t (1;22), which generates the RBM15-MKL1 fusion gene, is found in approximately 10% of pediatric acute megakaryoblastic leukemia cases. Given that PRMT1 downregulation is critical for megakaryocyte differentiation, we propose the use of the PRMT1 inhibitor furamidine to stimulate RBM15-MKL1-transformed human cord blood cells to undergo megakaryocyte differentiation.

**Materials and methods:** Human CD34<sup>+</sup> cells were purified from umbilical cord blood with anti-CD34 magnetic beads. Lentivirus-infected CD34<sup>+</sup> cells were sorted using flow cytometry. The methylcellulose colony replating assay was performed to evaluate the transformation efficiency. Cell viability was calculated using a CellTiter-Glo<sup>®</sup> luminescent cell viability assay kit.

**Results:** The simultaneous transduction of RBM15-MKL1 and MPL<sup>W515L</sup>, a mutated MPL gene found in AMKL patients, into human CD34<sup>+</sup> cells resulted in long-term growth in the presence of a cytokine mix that maintains a population of hematopoietic stem progenitor cells. Elevated expression of PRMT1 was detected in cells transduced with RBM15-MKL1 together with MPL<sup>W515L</sup>. The PRMT1 inhibitor furamidine (aka DB75) reversed the inhibition of RBM15-MKL1-mediated megakaryocytic differentiation and impeded the replating capability of the transformed cells.

**Conclusion:** PRMT1 facilitates the transformation induced by RBM15-MKL1, and inhibiting PRMT1 activity promotes MK differentiation. Given that furamidine has been used for treating trypanosomiasis in clinical trials and proven to be safe, using furamidine to treat AMKL may be a new curative option for RBM15-MKL1-associated leukemia.

**Keywords:** RBM15-MKL1; PRMT1; Acute Megakaryoblastic Leukemia

**Abbreviations:** PRMT1: Protein Arginine Methyltransferase 1; RBM15: RNA Binding Motif Protein 15; MKL1: Megakaryoblastic Leukemia 1; OTT-MAL: One Twenty-Two-Megakaryocytic Acute Leukemia; Spen: Split End; GATA1: GATA Binding Protein 1; RUNX1: Runt-Related Transcription Factor 1; TAL1: T-cell Acute Lymphocytic Leukemia Protein 1; JAK: Janus Kinase; MLL: Myeloid-Lymphoid Leukemia; EEN: Extra Eleven Nineteen; AML1: Acute Myeloid Leukemia 1

## Introduction

Acute megakaryoblastic leukemia (AMKL) is characterized by impaired terminal megakaryocytic differentiation and the accumulation of megakaryoblasts in bone marrow [1]. AMKL consists of approximately 13% of all pediatric leukemia cases [2]. AMKL patients are classified as Down syndrome (DS) leukemia and non-DS leukemia [3]. Chromosome translocations have been discovered in patients with non-DS leukemia. *RBM15-MKL1*, which is derived from the t (1; 22) translocation, fuses an almost full-length RBM15 protein (OTT) to the MKL1 protein (MAL). The t (1; 22) translocation accounts for approximately 13% of non-DS leukemia cases [4]. RBM15-MKL1 knock-in mice display aberrant hematopoiesis and develop low penetrant AMKL. Introducing a constitutively active thrombopoietin (TPO) receptor (MPL) mutant into RBM15-MKL1 knock-in bone marrow cells efficiently induced robust AMKL with a short latency [5].

Both the RBM15 and MKL1 genes are critical for megakaryocytic differentiation. RBM15 is a member of the Spen family, whose

members have 3 RNA recognition motifs and an SPOC domain [6]. RBM15 modulates RNA surveillance, transport and degradation through its RNA recognition motifs [7]. RNA splicing of some critical transcription factors involved in megakaryocytic differentiation such as GATA1, RUNX1, TAL1 and MPL are regulated by RBM15 [8]. RBM15 regulates Notch pathway through its C-terminal SPOC domain by binding to RBPJ, a subunit of Notch transcriptional regulatory complex. Conditional knockout of RBM15 in adult mice shows that RBM15 is required for the stress response of hematopoietic stem cells, and RBM15 knockout promotes the proliferation of megakaryocyte (MK) progenitor cells [9]. MKL1 is a transcriptional coactivator that belongs to the myocardin family. MKL1 resides in the cytoplasm and translocates into the nucleus to bind serum response factor (SRF) in response to cell differentiation signals [10]. MKL1 is upregulated during murine megakaryocyte differentiation, and MKL1-knockout mice leads to the increase in the number of megakaryocytic progenitors

**\*Corresponding author:** Liu Y, Department of Internal Medicine, Henan Cancer Hospital & Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China. Tel: 0086-371-65587791; E-mail: [yylu@zzu.edu.cn](mailto:yylu@zzu.edu.cn)

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[11]. The fusion of the RBM15 and MKL1 genes results in loss of their individual physiological functions and gain of function toward AMKL development [12]. RBM15-MKL1 fusion gene activates the Notch pathway via by interacting with RBPJ, a subunit of the NOTCH transcriptional regulatory complex. Activated Notch signaling has been implicated in both hematopoietic stem cell immortalization and tumorigenesis.

Protein arginine methyltransferase 1 (PRMT1) catalyzes asymmetric arginine methylation and accounts for the majority of enzymatic activity in cells [13]. PRMT1 facilitates tumor cell proliferation in myeloid leukemia, lymphoid leukemia, and lymphoma as well as promotes metastasis of solid tumors [14]. Several potent and selective PRMT1 inhibitors have been successfully developed [15]. One PRMT1 inhibitor, DB75, has been successfully used for treating parasite infections such as trypanosomiasis and leishmania and has been proven to be safe in mouse studies and clinical trials [16]. Inhibition of PRMT1 activity by DB75 promotes MK terminal differentiation. This study aimed to explore the feasibility of using either the PRMT1 inhibitor DB75 or furamidine to treat AMKL. The success of using DB75 to restore MK differentiation would lay the groundwork for future animal studies with patient-derived xenograft models.

## Materials and Methods

### Purification and culture of human CD34<sup>+</sup> cells

Human umbilical cord blood was collected from healthy pregnant women who provided informed consent. After separation with Ficoll-Paque PLUS (GE), CD34<sup>+</sup> cells were purified with anti-CD34 magnetic beads (Miltenyi Biotec, Bergisch Gladbach, Germany) in accordance with the manufacturer's instructions and cultured in Iscove's modified Dulbecco's medium (GIBCO) supplemented with 20% serum substitutes (BIT) (Stem Cell Technology, Canada) and a cytokine mixture (20 ng/mL TPO, 20 ng/mL interleukin-6, 100 ng/mL stem cell factor, 10 ng/mL Flt3 ligand; all from Peprotech). The purification achieved 95% purity for CD34<sup>+</sup> cells according to FACS analysis.

### Viral production and transduction

HEK293T cells were cultured in DMEM supplemented with 10% FBS containing 100 U/mL penicillin and 100 µg/ml streptomycin. For virus production, HEK293T cells were cotransfected with lentiviral plasmids and helper plasmids as previously described. Supernatant containing lentivirus was collected and concentrated using the PEG concentration method [17]. After transduction with concentrated lentivirus, FACS sorted GFP and mCherry double positive cells (BD FACSAria III). The data were analyzed with FlowJo software.

### Cells serial replating assays

Assays were performed using MethoCult H4100 medium (StemCell Technologies) supplemented with 20% BIT, 50 µM β-mercaptoethanol, 2 mM L-glutamine, 100 U/mL penicillin/streptomycin, and a human cytokine mixture (20 ng/mL TPO, 20 ng/mL interleukin-6, 100 ng/mL stem cell factor, 10 ng/mL Flt3 ligand; all from Peprotech), MethoCult containing 5000 cells was dispensed into one well of a 6-well plate. Colonies containing more than 50 cells were scored on day 10. Colonies were pooled together, and 5000 cells were used for replating.

### Flow cytometry analysis

For the megakaryocytic differentiation analysis, cells were stained with anti-CD41 and anti-CD42 antibodies (BD). The samples were analyzed within 1 hour after staining by a BD FACSCalibur machine.

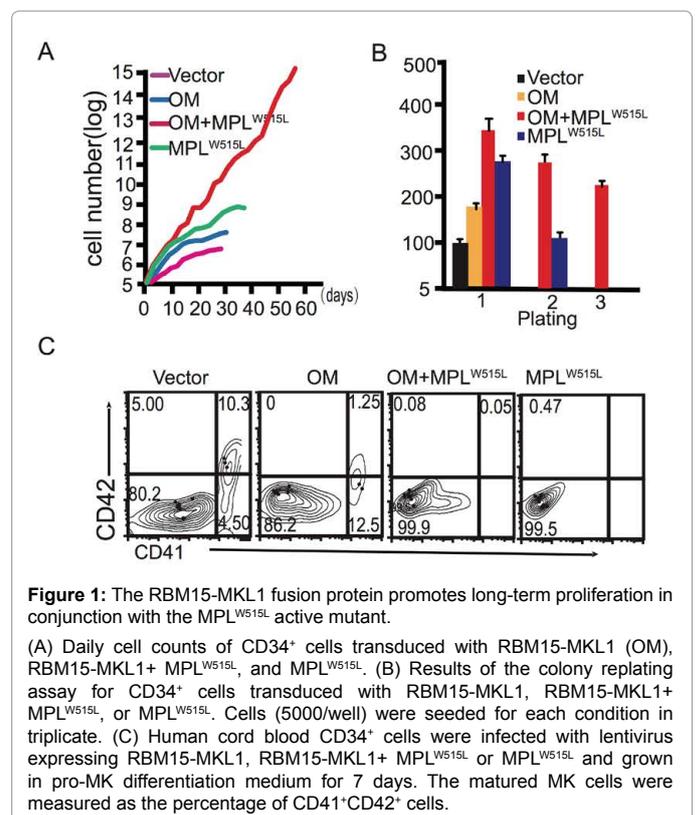
## Real-time Polymerase Chain Reaction (RT-PCR)

Total RNA was isolated from  $5 \times 10^5$  cells using an RNeasy Micro Kit (QIAGEN), and cDNA was reversed transcribed using the SuperScript® First-Strand Synthesis System (Invitrogen). RT-PCR was performed using SYBR® Green Real-time PCR Master Mix-Plus (Thermo Scientific). GAPDH was used as an internal control for normalization. The relative expression level was calculated by the  $\Delta(\Delta C_t)$  method, and all the results are expressed as the mean values ± standard errors from at least 3 independent experiments. Human PRMT1 forward primer: 5'-CCAGTGGAGAAGGTGGACAT-3', human PRMT1 reverse primer: 5'-CTCCCACCAGTGGATCTTGT-3'.

## Results

### The RBM15-MKL1 fusion protein supports long-term proliferation in cooperation with the MPL<sup>W515L</sup> active mutant

It is difficult to obtain samples with the RBM15-MKL1 fusion from patients due to the low incidence rate and young age (infants younger than one year old). Therefore, we asked whether RBM15-MKL1 might be able to transform CD34<sup>+</sup> cells isolated from human cord blood, which may partially mimic the pathological features of RBM15-MKL1 leukemia. Transduction with RBM15-MKL1 or MPL<sup>W515L</sup> alone cannot support cell proliferation for longer than 40 days. Transduction of RBM15-MKL1 into CD34<sup>+</sup> cells promotes long-term proliferation with the cooperation of the mutant MPL gene (Figure 1A). The serial replating assay showed that RBM15-MKL1 did not support replating for more than one round, while the cells expressing MPL<sup>W515L</sup> and RBM15-MKL support at least three rounds of replating (Figure 1B). This result implies that the RBM15-MKL1 fusion protein alone cannot fully transform normal hematopoietic stem/progenitor cells. This result is also agreeable with data published by Mercher et al., which



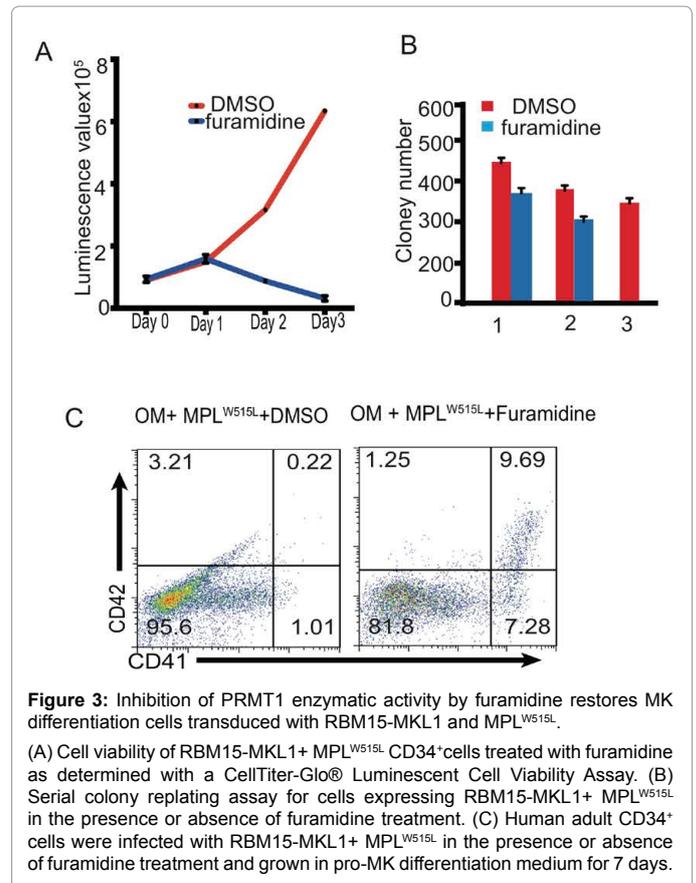
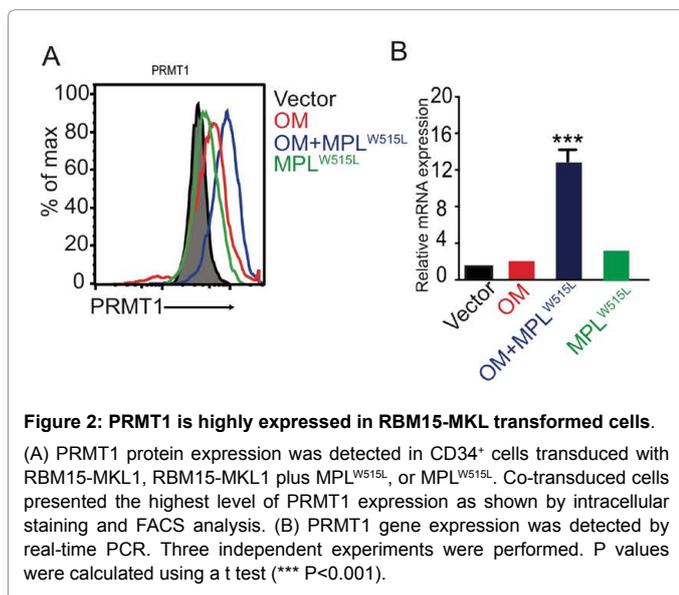
**Figure 1:** The RBM15-MKL1 fusion protein promotes long-term proliferation in conjunction with the MPL<sup>W515L</sup> active mutant.

(A) Daily cell counts of CD34<sup>+</sup> cells transduced with RBM15-MKL1 (OM), RBM15-MKL1+ MPL<sup>W515L</sup>, and MPL<sup>W515L</sup>. (B) Results of the colony replating assay for CD34<sup>+</sup> cells transduced with RBM15-MKL1, RBM15-MKL1+ MPL<sup>W515L</sup>, or MPL<sup>W515L</sup>. Cells (5000/well) were seeded for each condition in triplicate. (C) Human cord blood CD34<sup>+</sup> cells were infected with lentivirus expressing RBM15-MKL1, RBM15-MKL1+ MPL<sup>W515L</sup> or MPL<sup>W515L</sup> and grown in pro-MK differentiation medium for 7 days. The matured MK cells were measured as the percentage of CD41<sup>+</sup>CD42<sup>+</sup> cells.

demonstrated that RBM15-MKL1 alone can only cause low penetrant AMKL and that an additional mutation such as c-MPL<sup>W515L</sup> is needed for rapid progression to full-blown AMKL. Interestingly, we also found that the MPL mutant can further transform human CD34<sup>+</sup> cells as shown in the liquid culture and colony formation assays (Figure 1B). FACS analysis showed that the double transduced cells were CD41<sup>-</sup>, which implies that the differentiation is blocked at stages before cells are committed to the MK progenitor line (Figure 1C). Since RBM15-MKL1-initiated leukemias are CD41<sup>+</sup>, MPL<sup>W515L</sup> may not be a cooperative mutation in human patients. Nevertheless, the double transduced human cells may still offer some mechanistic insight on RBM15-MKL1-mediated leukemogenesis. Given that PRMT1 has been reported to be highly expressed in AMKL leukemia [18], we performed real-time PCR to determine the PRMT1 expression level in these cord blood cells transduced with RBM15-MKL1, MPL<sup>W515L</sup> or both oncogenes together. Strikingly, the PRMT1 expression levels were tenfold higher in cells transduced with both two oncogenes together (Figures 2A and 2B). Thus, we hypothesized that PRMT1 may be responsible for promoting the proliferation of RBM15-MKL1-transformed leukemia.

### The PRMT1 inhibitor furamidine promotes the differentiation of transformed CD34<sup>+</sup> cells

Furamidine (DB75) has been used as anti-parasite drug [19]. Recently, DB75 was demonstrated to inhibit PRMT1. Treatment of normal CD34<sup>+</sup> cells with DB75 promoted MK differentiation. Thus we speculated that DB75 might restore MK differentiation of cells transduced with RBM15-MKL1 and MPL<sup>W515L</sup>. To this end, we treated CD34<sup>+</sup> cells transduced with RBM15-MKL1 and MPL<sup>W515L</sup> with 1 μM of DB75. Within 3 days, the DB75-treated cells stopped growing and died (Figure 3A). Then, we performed the serial replating assay with the drug-treated cells. DB75 impeded colony formation at the third round of replating (Figure 3B). We subjected the transformed cells to MK differentiation by culturing the cells with high concentrations of TPO. As shown in Figure 1, the transformed cells could not proceed to terminal differentiation, while DB75 treatment resulted in terminal differentiation (Figure 3C).



### Discussion

The oncogenic role of the RBM15-MKL1 fusion protein in AMKL development has been demonstrated in the RBM15-MKL1 knock-in mouse mode. However, how RBM15-MKL1 transforms human cells has not been investigated. Given that RBM15-MKL1 mostly causes AMKL in patients younger than one year old, using human cord blood cells (which are at the fetal stage of hematopoiesis) may better mimic human AMKL. In this study, we used CD34<sup>+</sup> cells derived from human cord blood to investigate how RBM15-MKL1 drives leukemia development. Although most of the cases of DS AMKL and non-DS AMKL without the RBM15-MKL1 translocation carry either active kinase mutations in JAK1, JAK2, JAK3, MPL, KRAS, or NRAS or loss-of-function mutations in epigenetic genes, no cooperative mutations have been found for RBM15-MKL1-initiated leukemia [20]. Intriguingly, amplification of chromosome 19 has been associated with RBM15-MKL1-induced AMKL. Of note, PRMT1 is on chromosome 19. We speculate that high expression levels of PRMT1 may be responsible for facilitating AMKL development.

This study validates the notion that PRMT1 is involved in RBM15-MKL1-associated aberrant megakaryocyte differentiation and cell immortalization. A decline in PRMT1 expression was observed during normal megakaryocytic differentiation of human CD34<sup>+</sup> cells, and ectopic expression of PRMT1 negatively modulated megakaryocyte terminal differentiation. RBM15-MKL1 fusion and mutant MPL transformed human CD34<sup>+</sup> cells into cells with highly increased levels of PRMT1 expression. PRMT1 has been proven to contribute to tumorigenesis by regulating multiple molecular events [21,22]. PRMT1 specifically methylates arginine 3 on histone H4, which is

associated with transcription activation. PRMT1 can also methylate large numbers of non-histone substrates, including RBM15 and RUNX1, and is involved in normal and malignant hematopoiesis [23]. Thus, inhibition of PRMT1 activity may have profound effects on MK differentiation by altering multiple pathways.

The precise mechanisms involved in PRMT1-mediated AMKL are still elusive. The PRMT1 inhibitor can overcome RBM15-MKL1-induced block of megakaryocyte differentiation and repress cell growth. The oncogenic role of PRMT1 in mixed lineage leukemia (MLL) with the MLL-EEN fusion gene has been reported [24]. PRMT1 interacts with *AML1-ETO* and is crucial for AML1-ETO-mediated transformation [25]. Taken together, these studies suggest that PRMT1 inhibitors could be used to treat various types of acute myeloid leukemia. Furamidine has been used in clinical trials [26-28]. Overall, DB75 is well tolerated in animal studies. In the future, we will test DB75 in the AMKL mouse model. Therefore, DB75 may be a front runner as a PRMT1 inhibitor for cancer treatment.

## Contributors

SJ designed and performed the experiments, analyzed the data, and wrote the manuscript. ZY and MF performed the experiments and analyzed the data. SY and JS provided reagents and made suggestions. JZ, PZ, WZ, and HW performed the experiments. JM and YG analyzed the data and made suggestions. YL conceived and designed the project, analyzed the data and wrote the manuscript. All the authors read and approved the final manuscript.

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## Competing Interest

The authors declare no competing interests in the contents of this manuscript.

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