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POSTER ABSTRACTS

641.CHRONIC LYMPHOCYTIC LEUKEMIAS: BASIC AND TRANSLATIONAL

PRMT1 Promotes Chronic Lymphocytic Leukemia Progression Via Modulating Methylation of MAST1

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Introduction

As a member of the protein arginine N-methyltransferase family, protein arginine methyltransferase 1 (PRMT1) plays a crucial regulatory role in the etiology of malignant neoplasms. PRMT1-mediated protein methylation promoted the maintenance of acute myeloid leukemia, which revealed the promising potency of PRMT1 inhibitors. Recent study suggested that dysregulation of PRMT5 promotes Richter's transformation in chronic lymphocytic leukemia (CLL). However, the effects of PRMT1 in the tumorigenesis and progression of CLL still remained ill-defined. Hence, the aim of this study was to investigate the clinical significance and mechanisms of PRMT1 underlying the development of CLL.

Methods

Peripheral blood samples were collected from 79 newly diagnosed CLL patients (47 males and 32 females; age range 39-85 years, median 63 years) in Shandong Provincial Hospital CLL (SPHCLL) cohort with informed consent. CRISPR-Cas9 technology was used to stably knockout PRMT1 in CLL cells. A label free quantitative proteomics analysis was implemented to reveal the protein methylation mediated by PRMT1. Assessment of cell viability, apoptosis and cell cycle were analyzed by cell counting kit-8, annexin V-PE/7AAD and PI/ RNase staining, respectively. This study was approved by the Medical Ethics Committee of Shandong Provincial Hospital.

Results

This study examined the expression of PRMT1 in SPHCLL and GEO databases, and discovered the upregulation of PRMT1 mRNA in CLL cells. Aberrantly elevated expression of PRMT1 was observed in a cohort of newly diagnosed CLL patients than healthy donors in mRNA level (donors vs. CLL patients, 0.07±0.06 vs. 0.20 ±0.21, p=0.013). Furthermore, increased expression of PRMT1 was correlated with inferior prognosis in two long-term follow-up cohorts of CLL patients (HR=2.80, p=0.002, and HR=1.551, p=0.009).

To elucidate the functional significance of PRMT1 in CLL, we established stable PRMT1 knockdown cells using lentiviral shRNAs and PRMT1 knockout cells using CRISPR/Cas9 technology. The suppression of PRMT1 remarkably inhibited cell proliferation, induced cell apoptosis and blocked cell cycle at G1/S phase in CLL cells. Furthermore, it was observed that C7280948, a selective inhibitor of PRMT1, resulted in the defective proliferation of CLL primary cells in a dose-dependent manner. We subsequently performed pre-clinical investigations of C7280948 in the orthotopic CLL xenograft murine model. Notably, the administration of C7280948 significantly diminished the leukemia burden and induced the lessened degree of splenomegaly in comparison to the control group (Fig. 1A). Moreover, a reduction in the population of CLL cells was detected in bone marrow and spleen of mice treated with C7280948.

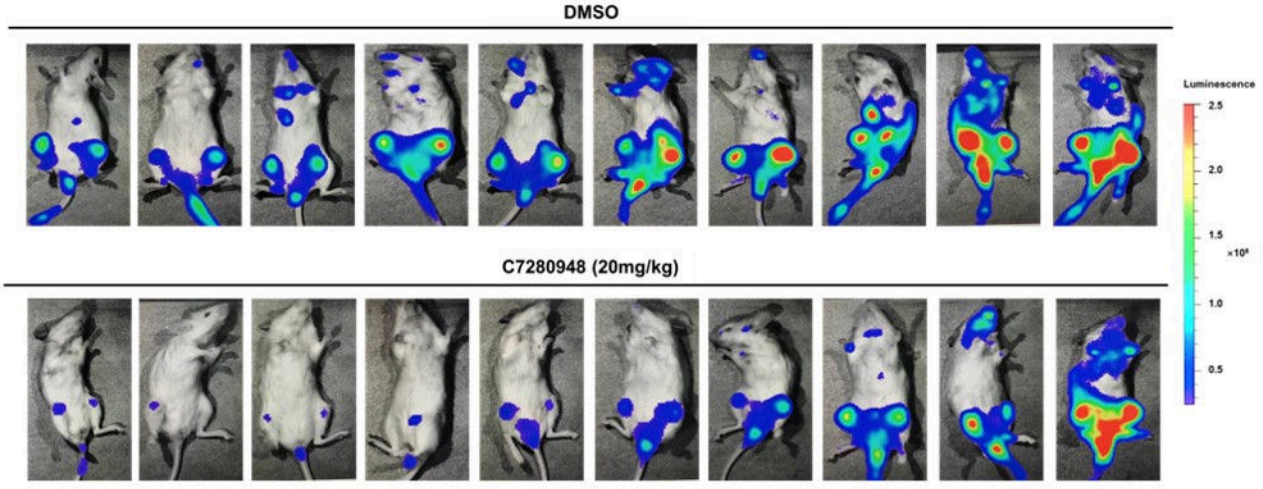
To decipher the role of PRMT1 in the pathogenesis of CLL, the label free quantitative proteomics analysis was conducted on PRMT1-deficent and control MEC1 cells. Knockdown of PRMT1 diminished asymmetric dimethylarginine of some proteins in CLL cells. In accordance with the results of proteomics analysis, microtubule associated serine/threonine kinase 1 (MAST1) was selected as a candidate target for further investigation. The methylation site of MAST1 protein was identified as R802 (Fig. 1B). Increased expression of MAST1 was correlated with inferior prognosis of CLL patients (p<0.001), indicating the essential role of MAST1 in the progression of CLL. These results supported the hypothesis that PRMT1 interacted with MAST1 and enhanced the activity of MAST1 via methylating this oncoprotein in CLL cells.

Conclusion

The present study provides robust evidence for the oncogenic function of PRMT1 in the pathogenesis of CLL, highlighting the potential therapeutic efficacy of the selective PRMT1 inhibitor C7280948. Collectively, the targeted inhibition of PRMT1 exhibits promising prospects for the management of CLL patients.

Figure 1

A



B

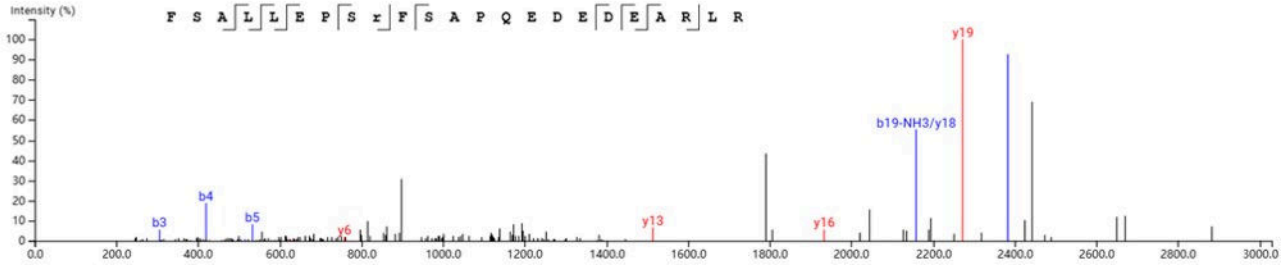


Figure 1

Disclosures No relevant conflicts of interest to declare.

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