


# VLX1570 induces apoptosis through the generation of ROS and induction of ER stress on leukemia cell lines

Nami Kurozumi<sup>1,2</sup> | Takayuki Tsujioka<sup>3</sup> | Mamoru Ouchida<sup>4</sup> | Kanae Sakakibara<sup>1</sup> | Takako Nakahara<sup>1</sup> | Shin-ichiro Suemori<sup>3</sup> | Masaki Takeuchi<sup>1</sup> | Akira Kitanaka<sup>1,3</sup> | Misako Shibakura<sup>2</sup> | Kaoru Tohyama<sup>1,3</sup> 

<sup>1</sup>Division of Medical Technology, Kawasaki University of Medical Welfare, Okayama, Japan

<sup>2</sup>Field of Medical Technology, Graduate School of Health Sciences, Okayama University, Okayama, Japan

<sup>3</sup>Department of Laboratory Medicine, Kawasaki Medical School, Okayama, Japan

<sup>4</sup>Department of Molecular Oncology, Graduate School of Medical, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan

## Correspondence

Kaoru Tohyama, Department of Laboratory Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki-City, Okayama 701-0192, Japan.

Email: ktohyama@med.kawasaki-m.ac.jp

## Funding information

A Kawasaki Medical School project grant, a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science.

## Abstract

A novel proteasome deubiquitinase inhibitor, VLX1570, has been highlighted as a promising therapeutic agent mainly for lymphoid neoplasms and solid tumors. We examined in vitro effects of VLX1570 on eight myeloid and three lymphoid leukemia cell lines. From cell culture studies, 10 out of 11 cell lines except K562 were found to be susceptible to VLX1570 treatment and it inhibited cell growth mainly by apoptosis. Next, to identify the signaling pathways associated with apoptosis, we performed gene expression profiling using HL-60 with or without 50 nmol/L of VLX1570 for 3 hours and demonstrated that VLX1570 induced the genetic pathway involved in “heat shock transcription factor 1 (HSF1) activation”, “HSF1 dependent transactivation”, and “Regulation of HSF1 mediated heat shock response”. VLX1570 increased the amount of high molecular weight polyubiquitinated proteins and the expression of HSP70 as the result of the suppression of ubiquitin proteasome system, the expression of heme oxygenase-1, and the amount of phosphorylation in JNK and p38 associated with the generation of reactive oxygen species (ROS) induced apoptosis and the amount of phosphorylation in eIF2 $\alpha$ , inducing the expression of ATF4 and endoplasmic reticulum (ER) stress dependent apoptosis protein, CHOP, and the amount of phosphorylation slightly in IRE1 $\alpha$ , leading to increased expression of XBP-1s in leukemia cell lines. In the present study, we demonstrate that VLX1570 induces apoptosis and exerts a potential anti-leukemic effect through the generation of ROS and induction of ER stress in leukemia cell lines.

## KEYWORDS

acute myeloid leukemia, proteasome deubiquitinase, VLX1570, reactive oxygen species, endoplasmic reticulum stress

## 1 | INTRODUCTION

Acute myeloid leukemia (AML) is characterized by clonal expansion of myeloid blasts in the peripheral blood and bone marrow.<sup>1</sup>

The prognosis of patients with AML has been improved by advances in hematopoietic stem cell transplantation (HSCT).<sup>2,3</sup> Dombret and Gardin reported that more than 80% of younger patients with AML reach complete remission with 5-year overall survival up to 40%.<sup>4</sup>

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