XPO1 Inhibitor Selinexor Induces Heme Oxygenase-1 Mediated p53-Dependent Mitochondrial Ferroptosis in Chronic Lymphocytic Leukemia

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INTRODUCTION

- In previous studies, we have confirmed that XPO1 is highly expressed in chronic lymphocytic leukemia (CLL) and is associated with a poor prognosis. The XPO1 inhibitor selinexor can target XPO1 to exert anti-tumor effects in CLL
- Currently, the mechanism of selinexor in CLL remains unknown.

OBJECTIVES

- This study was to evaluate the underlying molecular basis for selinexor in CLL cells with wild-type and mutant p53.

MATERIALS AND METHODS

- Functional assessments included Cell Counting Kit-8, reactive oxygen species (ROS) detection, and Fe^{2+} detection.
- Molecular profiling, including RNA sequencing, dual-luciferase reporter assays, western blot, and quantitative reverse transcription PCR (qRT-PCR), was performed to evaluate the effects of selinexor on CLL cells.
- Subcellular protein distribution was assessed through immunofluorescence staining.
- Underlying mechanisms were investigated using small molecule inhibitors, CRISPR-Cas9-mediated gene knockout, and shRNA-mediated knockdown.

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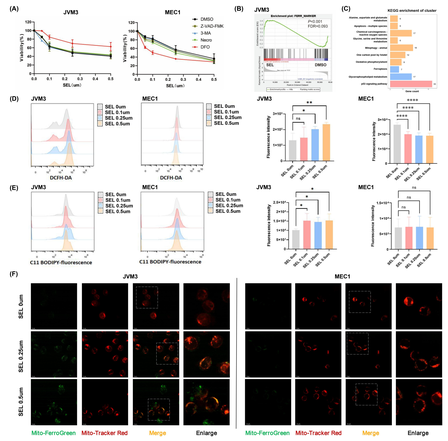
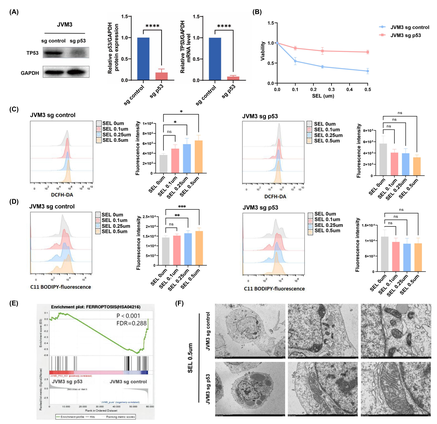
Figures

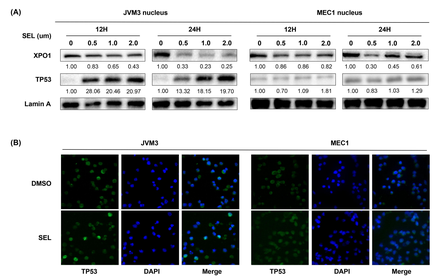
1.Selinexor Inhibits Proliferation of p53 Wild-type CLL Cells through Ferroptosis



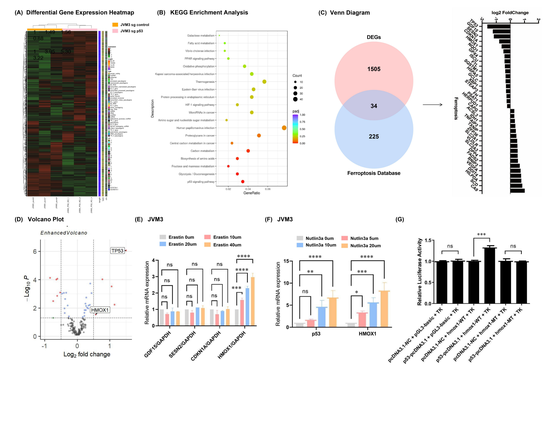
2.Selinexor Induced Ferroptosis in CLL Cells Depends on p53



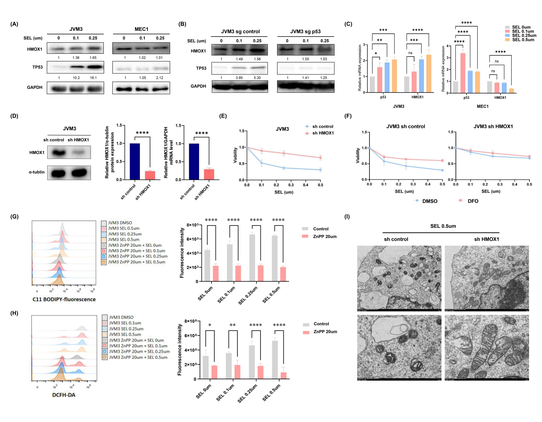
3.Selinexor Activates the p53 Pathway by Inhibiting the Nuclear-cytoplasmic Transport of p53 in CLL Cells



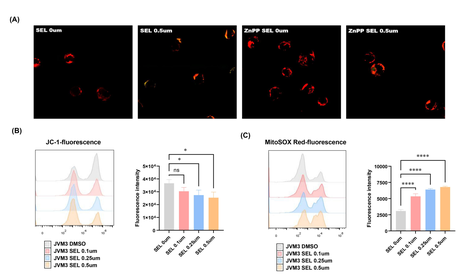
4. THemoglobin Oxygenase 1 (HMOX1) is a Downstream Gene of p53 Regulating Ferroptosis in CLL



5. p53-HMOX1 axis mediates selinexor-induced ferroptosis



6. HMOX1 Regulates Ferroptosis by Modulating Mitochondrial Iron Metabolism and Function



Results

- The XPO1 inhibitor selinexor induced a ferroptotic process in p53 wild-type CLL cells, accompanied by increased levels of ROS, lipid peroxidation, and Fe^{2+}.
- TP53 knockout in JVM3 CLL cells using CRISPR-Cas9 reduced selinexor-induced ferroptosis, and transcriptomic profiling confirmed the downregulation of the p53-dependent ferroptosis pathway. Selinexor enhanced the nuclear accumulation of p53 in wild-type JVM3 CLL cells, thereby activating the p53 signaling pathway.
- Functional validation demonstrated that selinexor-induced mitochondrial ferroptosis in CLL was dependent on p53-HMOX1 axis activity. HMOX1 inhibition and shRNA interference attenuated the effect of selinexor on cell viability and ferroptosis. The Mito-FerroGreen fluorescent probe revealed that the HMOX1 inhibitor ZnPP could counteract selinexor-induced mitochondrial Fe2+ overload, indicating that the regulation of HMOX1 mediated the mitochondrial redistribution of iron.

CONCLUSION

- We investigated, for the first time, the targeting of XPO1 by selinexor-induced ferroptosis in CLL cells through a p53-dependent pathway.
- The p53-HMOX1 axis orchestrated ferroptosis by preferentially directing iron to mitochondria and inducing mitochondrial dysfunction.

ACKNOWLEDGEMENT

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