(PB2557) HDAC6 INHIBITOR ACY-738 INDUCES FERRITINOPHAGY-MEDIATED FERROPTOSIS IN LEUKEMIA

Topic: 01. Acute lymphoblastic leukemia - Biology & translational research

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Background

Leukemia is one of the most challenging hematological system tumor with poor prognosis. Frequent recurrence and drug resistance seriously restrict the clinical efficacy. Ferroptosis is an iron-dependent form of regulated cell death and plays a vital role in tumor suppression. Ferroptosis inducing agents have been studied extensively as a novel promising way to fight against therapy resistant cancers. The aim of this study is to investigate the mechanism of ACY-738, a kind of HDAC6 inhibitor, as a novel ferroptosis inducer in tumor suppression.

Methods

The response of cells to ACY-738 was assessed by cell viability assay, EdU assay and clonogenic assay. Proteomic analysis and metabolomic analysis were used to identify downstream targets of GD3s. RNA sequencing analysis and metabolomic analysis was used to explore the possible biological processes, molecular functions and signaling pathways of ACY-738. The morphological changes of mitochondria were observed by transmission electron microscope. The level of ferroptosis was determined by the lipid peroxidation assay, cystine uptake assay, glutathione content detection assay and the level of free iron. The mechanism was verified by molecular approaches including Western blot, quantitative real-time PCR and immunofluorescence.

Results

ACY-738 inhibited the proliferation, DNA synthesis and colony formation of leukemia cells, and induced an oxidative cellular microenvironment resulting in ferroptosis of leukemia cells. ACY-738-induced ferroptosis was accompanied with the decreased of cystine uptaking, attenuation of glutathione levels and increased of lipid peroxidation. ACY-738 also increased the level of intracellular free iron and the level of labile iron pool, which also led to ferroptosis. Mechanistically, ACY-738 inhibited the binding of HDAC6 and NCOA4, reduced the ubiquitination degradation of NCOA4, increased the expression of autophagy-related protein LC3B and P62, promoted the autophagic degradation of NCOA4-mediated ferritin, led to the increase in the labile iron pool. ACY-738 also inhibited the expression of SLC7A11, resulting in decreased intracellular cystine levels and attenuation of glutathione levels, indirectly inhibiting GPX4 activity, which promoted lipid peroxidation and ultimately inducing ferroptosis in cells.

Summary/Conclusion

In summary, we provided the evidence that HDAC6 inhibitor ACY-738 inhibited the proliferation and induced ferroptosis in leukemia cells. Mechanistically, ACY-738 induces ferroptosis through inhibits the binding of HDAC6 and NCOA4 by targeting HDAC6, reduces the ubiquitination degradation of NCOA4, and promotes NCOA4-mediated ferritinophagy. ACY-738, identified as a novel ferroptosis inducer, may be effective chemosensitizer that can expand the efficacy and range of chemotherapeutic agents.

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