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Chapter

Ferroptosis in Leukemia: Lessons and Challenges

Baoquan Song and Leisheng Zhang

Abstract

Ferroptosis is a newly defined programmed cell death (PCD) process with the hallmark of the accumulation of iron-dependent lipid peroxidation, which is more immunogenic over apoptosis. Ferroptosis shows great potential as a therapeutic target against acute kidney injury (AKI), cancers, cardiovascular diseases, neurodegenerative diseases, and hepatic diseases. Accumulating evidence has highlighted that ferroptosis plays an unneglectable role in regulating the development and progression of multiple pathologies of leukemia including acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), and chronic lymphocytic leukemia (CLL). Herein, we focus on the state-of-the-art renewal in the relationship of ferroptosis with leukemia. Meanwhile, this chapter further highlights the iron, lipid and amino acid metabolism, as well as ferroptosis-based molecular mechanisms. Collectively, we summarize the contribution of ferroptosis to the pathogenesis of leukemia and discuss ferroptosis as a novel therapeutic target for different types of leukemia.

Keywords: ferroptosis, programmed cell death, leukemia, metabolism, novel therapeutic targets, lipid peroxides

1. Introduction

Ferroptosis is a new type of iron-dependent programmed cell death (PCD) that was first reported by Dixon et al. in 2012, which is initiated by lipid peroxidation and terminates in toxic lipid peroxidation and mitochondrial dysfunction [1, 2]. As a new form of PCD, ferroptosis can be distinguished from other types of cell death such as necrosis, pyrolysis, apoptosis, and autophagy in regard to morphology and biochemistry [3, 4]. As to the morphological characteristics, the major manifestation of ferroptosis is increase in mitochondrial membrane density, unspoilt cytomembranes, cell volume shrinkage, decline or even deficiency in mitochondrial cristae, outer membrane rupture and mitochondrial membrane crumpling, and normal cellular nucleus size with unconsolidated chromatin [5, 6]. As to the biochemical characteristics, ferroptosis results from the accumulation of iron-catalyzed lipid-based reactive oxygen species (ROS), which is commonly initiated by either the loss of the activity of the lipid repair enzyme named glutathione peroxidase 4 (Gpx4) or the inactivation of the antioxidant defenses depending on the cellular glutathione (GSH) [7]. As to the genetic characteristics, a considerable number of genes have been indicated to

modulate ferroptosis by acting as inhibitors or inducers, which can be divided into the system Xc-, Gpx4, GSH, lipid peroxidation-associated genes, and iron metabolism regulation-associated genes on the basis of the variations in targets, whereas the specific regulatory mechanisms of ferroptosis still need to be further explored [8].

Taken together, ferroptosis has been regarded with initiation by the failure of the aforementioned GSH-dependent antioxidant defenses, which thus results in the uncontrolled process during lipid peroxidation and the concomitant cell death [9, 10]. Similarly, the out-of-balance phenomenon between GSH-dependent Gpx4 inactivity and the iron-catalyzed lipid ROS production eventually triggers the occurrence of ferroptosis. Accordingly, the lipophilic antioxidants and iron chelators can effectively suppress the process of ferroptotic cell death [11]. The former inhibits the initiation and accumulation of the lipid peroxidation by capturing or eliminating targeting lipoxygenase and free radicals, including ferrostatin-1 (Fer-1), *N*-acetylcysteine (NAC), vitamin E, and liproxstatin-1 (Lip-1) [12]. The latter can efficaciously prevent the aforementioned iron-catalyzed-associated lipid peroxidation by acerating the depletion of free iron, including deferiprone (DFP) and deferoxamine (DFO) [13]. In spite of the rapid development of the multifaceted assumptions and considerable validations, the systematic and detailed molecular mechanisms of ferroptosis are still far from being fully clarified. The regulatory mechanisms of ferroptosis are complicated and involve a variety of metabolic networks and signaling pathways, including abnormal iron metabolism, lipid metabolism, amino acid metabolism, and signaling pathways associated with ferroptosis. For instance, a number of studies have reported the involvement of several signaling pathways with ferroptosis such as ferritinophagy, iron and amino acid metabolism, cell adhesion, and Keap1/Nrf2, mTOR, and p53 signaling pathways [14–16].

Nowadays, ferroptosis has been considered to perform a critical role in various diseases and pathologies, such as cancer, stroke, cardiomyopathy, kidney and liver injury, and neurodegeneration [17, 18]. Meanwhile, both the indicated inhibitors and activators have been continuously identified and introduced to explore the molecular mechanisms of ferroptosis, which collectively benefit the development of novel therapeutic strategies for the administration of ferroptosis-related diseases and pathologies [19]. In the meantime, accumulating evidence has indicated the changes in iron metabolism during leukemia, which thus has been considered as a crucial feature as well. To date, high oxidative stress and high iron requirements are identified with association to the alteration of iron metabolism during leukemia, which thus suggests that leukemia cells are more vulnerable to variations in ROS and iron levels when compared with the normal cells [20]. Therefore, targeting iron metabolism may provide new insights into approaches to the treatment of leukemia.

2. Ferroptosis and leukemia

Leukemia is a group of heterogeneous hematopoietic stem cell (HSC) malignancies. It is characterized by aberrant accumulation of undifferentiated blasts capable of unrestrained proliferation in the bone marrow, which interferes with the production of normal blood cells. Leukemic cells uniquely possess the innate ability for migration and invasion. Differentiated, malignant leukocytes retain the benign leukocytes' capacity for cell motility and survival in the circulation, while acquiring the potential for rapid and uncontrolled cell division. Currently, a variety of cancer cells of hematological malignancies (e.g., multiple myeloma, leukemia, and lymphoma) have been

identified to be sensitive to ferroptosis because large amounts of iron are acquired by leukemia cells for the maintenance of rapid growth and proliferation. As a consequence, targeting iron metabolism holds the potential to supply new insights into developing novel approaches for the administration of leukemia.

As a cancer of the bone marrow and blood cells, leukemia threatens human health seriously. Recent insights into iron metabolism along with the recent discovery of ferroptosis have opened new avenues in the field of antitumor therapies. Emerging evidence has revealed that ferroptosis is essentially a nexus among metabolism, redox biology, and diseases including cancers. The discovery of ferroptosis is a major breakthrough in the development of cancer treatments. Therefore, targeting ferroptosis may provide new insights into approaches to the treatment of leukemia. Leukemia is classified into four main subgroups, including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphoblastic leukemia (CLL). Therefore, we focus on these entities in this chapter.

2.1 Ferroptosis in acute myeloid leukemia

AML is the most common type of leukemia in adults, which is characterized by the rapid growth of abnormal lineage-specific hematopoietic precursor cells that do not differentiate into functional granulocytes or monocytes during hematopoiesis in the bone marrow microenvironment [21–24]. As a classical paradigm of myeloid disease with multiple life-threatening complications, AML is characterized by a significant reduction of physiological differentiation of hematopoietic stem and progenitor cells (HSPCs) toward myeloid and lymphoid lineages in parallel with aberrant activation of pathological hematopoiesis that is dominated by the continuous accumulation of the dysfunctional leukemic blast populations [25, 26]. Despite the dramatic progresses in exploring the pathogenesis and exploring advanced targeted therapies, the majority of the AML patients are still bearing immune dysregulation and the concomitant outcomes [25]. Long-term survival remains limitation with the standard-of-care chemotherapies combining anthracyclines with cytarabine. Development of resistance to chemotherapeutic agents is a major hurdle in the effective treatment of patients with AML [27]. New therapies are needed to improve chemotherapy efficacy in AML [25, 28]. Meanwhile, many endeavors have been made to ascertain *de novo* biomarkers and improve risk stratification and prognostic assessment in different AML subgroups [21]. However, more and more studies have proved that ferroptosis is closely related to the pathophysiology of AML and thus shed light on studying the pathogenesis of AML and search for new therapeutic targets.

A variety of molecular and pathological changes in ferroptosis have been observed in experimental AML models and samples from AML patients (**Table 1**). Among ferroptosis-related genes (FRGs), GPX-1, GPX-3, GPX-4, and GPX-7 were highly expressed in *n* AML patient samples and associated with poorer prognosis of overall survival (OS) [30]. AKR1C2 and SOCS1 are promising biomarkers for predicting prognosis in patients with AML [31]. Huang et al. [32] established a prognostic model of 12-FRGs in AML. The model successfully divided patients into high- and low-risk (LR) patient groups with mean OS as the basis. Wei et al. [15] showed that ferroptosis-related genes (FRGs), DPP4 and TFRC, act as biomarkers for predicting and diagnosing AML, and their expression levels also have significant correlations with drug resistance in AML. Other markers of ferroptosis, among the 12 ferroptosis-related genes (PHKG2, HSD17B11, STEAP3, HRAS, ARNTL, CXCL2, SLC38A1, PGD, ENPP2, ACSL3, DDIT4, and PSAT1), were screened to generate a prognostic model,

Leukemia	FRGs	Risks	Highlights of the study	Ref.
AML	GPX-1, -3, -4, and -7	Poor prognosis	The study offered novel insights into the differential expression and prognostic potential of the GPX family in AML.	[12]
	ACSL6 and G3BP1	Favorable prognosis	FRG risk model may be beneficial to the precision immunotherapy of AML patients in the future, especially those of HR groups.	[14]
	GPX4, CD44, FH, CISD1, SESN2, LPCAT3, AIFM2, ACSL5, HSPB1, and SOCS1	Favorable prognosis		
	CHAC1, CISD1, DPP4, GPX4, AIFM2, SQLE, PGD, and ACSF2	Poor prognosis	A novel ferroptosis-related prognostic model for outcome prediction and risk stratification in AML was conducted and validated.	[15]
	ZFPM2, ZNF560, ZSCAN4, HMX2, HRASLS, LGALS1, LHX6, CCL23, and FAM155B	Poor prognosis	The identified genes were affected by ferroptosis and develop a prognostic risk-scoring model to predict patients' survival at the genetic level.	[16]
	MXRA5, PCDHB12, PRINS, TMEM56, TWIST1, ASTN1, DLL3, EFNB3, and FOXL1	Favorable prognosis		
	AP001266.2, AC007383.2, AC008906.1, AC026771.1, and KIF26B-AS1	Favorable prognosis	Seven novel ferroptosis-related lncRNA signatures were established to accurately predict the prognosis of AML.	[17]
	AC133961.1 and AF064858.3	Poor prognosis		
	AKR1C2 and SOCS1	Poor prognosis	A prognostic risk model that included AKR1C2 and SOCS1 predicted outcomes in AML patients.	[18]
	DNAJB6 and HSPB1	Poor prognosis	Potential targets and new research ideas for the treatment and early detection of AML were identified.	[19]
	HIVEP3	Poor prognosis	HIVEP3 is a *de novo* independent prognostic indicator and the crosstalk between HIVEP3 and ferroptosis signaling pathways.	[20]
	Dipetidyl peptidase-4	Poor prognosis	DPP4 as a biomarker for predicting and diagnosing AML influences drug resistance in AML.	[21]
CML	TP63, STEAP3, NQO1, and ELAVL1	Poor prognosis	Cysteine depletion serves as a potential therapeutic strategy for overcoming chemotherapy resistance in CML.	[29]
	PRKAA1, HELLS, FANCD2, and CDKN2A	Favorable prognosis		

Table 1.
Bioinformatics studies predicting prognosis of leukemia patients based on the expression of ferroptosis-related genes

which stratified patients into a low- (LR) or high-risk (HR) group [33]. Another study showed that 18 signature genes, including DLL3, EFNB3, ZSCAN4, ASTN1, FAM155B, CCL23, ZFPM2, FOXL1, HMX2, LGALS1, LHX6, PCDHB12, MXRA5, HRASLS, TMEM56, PRINS, TWIST1, and ZNF560, were unified for the development of establishing the prognostic risk-scoring model. With the aid of the model, AML patients can be grouped into high-risk and low-risk groups, and those inpatients with low risk consistently revealed preferable survival over the high-risk inpatients [34]. In another study, investigators have identified and verified seven ferroptosis-related lncRNA signatures (AP001266.2, AC133961.1, AF064858.3, AC007383.2, AC008906.1, AC026771.1, and KIF26B-AS1) with independent prognostic value in patients with AML (**Table 1**) [35]. In summary, we conducted and validated a novel ferroptosis-related prognostic model for outcome prediction and risk stratification in AML, with great potential to guide individualized treatment strategies in the future [31, 36–38].

Currently, ferroptosis has been characterized by the well-established iron-dependent accumulation of the lipid hydroperoxides, which eventually leads to the severe impairments of the mitochondrial outer membrane as well as the decrease of mitochondria crista. Interestingly, cancer cell death has been proved to be involved in ferroptosis as well. Therewith, new treatment remedies by developing effective activators and inhibitors targeting ferroptosis will benefit the development of novel treatment paradigms for AML patients. As early as 2015, researchers found that the ferroptosis inducer Erastin enhances sensitivity of acute myeloid leukemia cells to chemotherapeutic agents [39]. Later, researchers demonstrated that DHA would induce autophagy and ferroptosis in AML cell lines and revealed the role of iron metabolism in DHA-induced cell death [40]. High mobility group box 1 (HMGB1) is a novel regulator of ferroptosis *via* the RAS-JNK/p38 pathway and a potential drug target for therapeutic interventions in leukemia. It plays an important role in leukemia pathogenesis and chemotherapy resistance [29]. Typhaneoside (TYP) is a major flavonoid in the extract of pollen typhae, showing significant biological and pharmacological effects. Zhu et al. [24] found that TYP significantly triggered autophagy in AML cells by promoting the activation of AMP-activated protein kinase (AMPK) signaling, contributing to ferritin degradation, ROS accumulation, and ferroptotic cell death ultimately. APR-246, also known as PRIMA-1MET, is a promising new therapeutic agent that targets TP53-mutated cancers. The association of APR-246 with induction of ferroptosis (either by pharmacological compounds or by genetic inactivation of SLC7A11 or GPX4) had a synergistic effect on the promotion of cell death, both *in vivo* and *ex vivo* [41]. circKDM4C is negatively associated with AML, and the downregulated circKDM4C leads to AML progression, which otherwise induces ferroptosis by regulating has-let-7b-5p and P53. This may be explored further to develop a potential AML therapy [42]. Aldehyde dehydrogenase 3a2 protects AML cells from oxidative death and the synthetic lethality of ferroptosis inducers. Combination of Aldh3a2 inhibition with ferroptosis inducers or with standard AML induction chemotherapy deserves further consideration as a cancer therapy [43]. Subsequent studies verified that HMOX1 was a critical target in honokiol-induced ferroptosis [44]. These results reveal that honokiol is an effective antileukemia agent in AML cell lines and may be a potential ferroptosis activator in AML.

2.2 Ferroptosis in acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) is a malignant clonal disorder of lymphoblastic hematopoiesis with high heterogeneity [45, 46]. Survival rates of ALL have

improved remarkably by intensive induction chemotherapy, with complete remission (CR) rates of up to 80%. However, relapse occurred in patients ranging from 25% to 35% [47]. Interestingly, ferroptosis is suggested to be a promising strategy for cancer treatment and therefore should also be evaluated in ALL [48, 49].

After the exploration of the potential role of ferroptosis in Ph-neg B-ALL with the clinical data and the RNA-seq results of 80 Ph-neg B-ALL, a Cox regression model based on 8 FRGs (ALOX15, ATP5G3, CARS, CDKN1A, LPCAT3, SAT1, SLC1A5, and TFRC) was established to help evaluate the prognosis of Ph-neg B-ALL patients [50]. Lukas et al. reported that the glutathione (GSH) peroxidase 4 (GPX4) inhibitor RSL3 triggers lipid peroxidation, production of reactive oxygen species (ROS) and cell death in ALL cells. Importantly, LOX inhibitors, including the selective 12/15-LOX inhibitor Baicalein and the pan-LOX inhibitor nordihydroguaiaretic acid (NDGA), protect ALL cells from RSL3-induced ferroptosis [51]. Artesunate (ART), a widely used antimalarial compound, exerted potent anti-ATLL effects through inducing reactive oxygen species production, resulting in cell death mediated by apoptosis, ferroptosis, and necroptosis [52]. Greco et al. [53] reported that sulforaphane (50 μM) induced U-937 cell ferroptosis through depletion of glutathione (GSH), decreased GSH peroxidase 4 protein expression, and lipid peroxidation. PAQR3 (also known as RKTG) has been proved to take part in many human cancers by acting as a tumor suppressor. Jin and Tong [48] showed PAQR3 inhibited proliferation and aggravated ferroptosis in ALL through modulation of Nrf2 stability. This study suggested that PAQR3 may serve as an effective biological marker for ALL treatment. Meanwhile, Hydnocarpin D (HD) is a bioactive flavonolignan compound that possesses promising antitumor activity, although accumulation of lipid ROS and decrease of GSH and GPX4, while inhibition of autophagy, impeded ferroptotic cell death [54]. Poricoic acid A (PAA) is the main chemical constituent on the surface layer of the mushroom Poria Cocos and exerts protective effects against various diseases. PAA treatments also provoked ferroptosis in T-ALL cells with reduced glutathione (GSH) levels and elevated malonaldehyde (MDA) content through inducing autophagic cell death and ferroptosis [55]. Yang et al. provided the first direct evidence that circ_0000745 promoted glycolytic metabolism and cell cycle progression but suppressed the occurrence of ferroptosis and apoptosis of acute lymphoblastic leukemia (ALL) cells *via* orchestrating the miR-494-3p/NET1 axis. That is, the Circ_0000745/miR-494-3p/NET1 axis might serve as a novel potential target for the treatment and diagnosis of ALL as well [56]. Another study found that FBXW7 was adequate to participate in degrading VDAC3 via modulating ubiquitination of cells to promote Erastin-induced ferroptosis during ALL, which could explain the potentially regulatory link between ferroptosis and autophagy. Moreover, Zhu et al. [49] also demonstrated the value and impact of the combination of Erastin and Rapa for ALL management both *in vivo* and *in vitro*.

2.3 Ferroptosis in chronic leukemia

Chronic leukemias are composed of a broad spectrum of subtypes such as including chronic monocytic leukemia, chronic mylocytic leukemia (juvenile, adult, and familial), chronic myelomonocytic leukemia, and chronic lymphocytic leukemia (CLL), which collectively account for lower than 5% of the childhood hematologic malignancies [57–59]. Recently, some studies have revealed the prognostic value of ferroptosis-related genes in chronic leukemia. For instance, Gong et al. indicated that ferroptosis-related genes can be used to stratify CLL patients based on overall

survival (OS) (**Table 1**). Meanwhile, they developed a risk signature containing eight ferroptosis-related genes for predicting the OS of CLL patients [60].

Several reports have shown the potential of triggering ferroptosis for chronic leukemia therapy, particularly for eradicating aggressive malignancies that are resistant to traditional therapies [60–63]. For decades, cysteine metabolism has been identified to have a critical role in cancer cell proliferation and survival, and cysteine depletion has been indicated to inhibit cancer growth and induce tumor cell ferroptosis. Furthermore, Liu et al. [64] have recently showed that cysteine depletion can induce ferroptosis in CML cells and TXNRD1 may be a key regulator gene. This illustrates that cysteine metabolism-induced ferroptosis may be a new idea for the treatment of CML except chemotherapy. Meanwhile, Song et al. [65] found that ferroptosis was involved in imatinib mesylate (IMA)-induced cardiotoxicity during the treatment of CML. In detail, they verified that IMA could downregulate Nrf2 expression but upregulate the P53 and TfR expression and thus increase the cellular ROS and iron, which collectively provided evidence for ferroptosis participation in IMA-induced cardiotoxicity and highlighted ferroptosis as a novel target in IMA-exposed patients.

3. Conclusions and perspectives

Ferroptosis is a newly discovered form of regulated cell death. Iron-dependent lipid peroxidation is a major driver of ferroptosis, and ferroptosis may also occur in leukemia. Ferroptosis is critically involved in the pathogenesis of various leukemia, including acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia and chronic lymphocytic leukemia. With ongoing research, prognostic value of ferroptosis-related genes and potential therapeutic strategy for overcoming chemotherapy resistance are likely to become effective therapeutic strategies for leukemia.

Acknowledgements

The authors would like to thank the members of The First Affiliated Hospital of Soochow University, Gansu Provincial Hospital, Chinese Academy of Sciences (CAS), Hefei Institute of Physical Science, and Institute of Health-Biotech, Health-Biotech (Tianjin) Stem Cell Research Institute Co., Ltd., for their technical support. This study was supported by grants from the National Natural Science Foundation of China (82260031, 81700119, and 81900175), Natural Science Foundation of Jiangsu Province (BE2018652, BK20201168, and BK20190181), the project Youth Fund funded by Shandong Provincial Natural Science Foundation (ZR2020QC097), science and technology projects of Guizhou Province (QKH-J-ZK[2021]-107), the project Youth Fund funded by Jiangxi Provincial Natural Science Foundation (S2021QNJJL0277), Jiangxi Provincial Key New Product Incubation Program from Technical Innovation Guidance Program of Shangrao city (2020G002 and 2020K003), Jiangxi Provincial Novel Research & Development Institutions of Shangrao City (2022AB003, 2020AB002, and 2021F013), Natural Science Foundation of Jiangxi Province (20212BAB216073), the 2021 Central-Guided Local Science and Technology Development Fund (ZYYDDFFZZJ-1), and the Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (2019PT320005).

Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

Not applicable.

Abbreviations

ROS	reactive oxygen species
AML	acute myeloid leukemia
ALL	acute lymphoblastic leukemia
Gpx4	glutathione peroxidase 4
DFP	deferiprone
DFO	deferoxamine
NAC	*N*-acetylcysteine
Fer-1	ferrostatin-1
Lip-1	liproxstatin-1
CML	chronic myeloid leukemia
CLL	chronic lymphoblastic leukemia
OS	overall survival
CR	complete remission
AMPK	AMP-activated protein kinase
HMGB1	high mobility group box 1
HD	Hydnocarpin D
PAA	poricoic acid A
GSH	glutathione
NDGA	nordihydroguaiaretic acid
HSPCs	hematopoietic stem and progenitor cells
IMA	imatinib mesylate
TYP	typhaneoside

Ferroptosis in Leukemia: Lessons and Challenges
DOI: http://dx.doi.org/10.5772/intechopen.108576

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