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Ferroptosis in Treatment of Drug-Resistant Leukemia

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Abstract. The major difficulty in leukemia treatment is drug resistance. Novel therapeutic approaches are being investigated to improve treatment efficiency. One of the research interests is the induction of ferroptosis, that bypasses many potential mutation sites in leukemic cells that spared them from apoptosis. Recent studies suggested that AML exhibits positive correlation with Nrf2 activity which triggers improved antioxidative defense mechanism of the cell, inhibiting this pathway enhances cellular ferroptosis sensitivity. In ALL, mutated FSP1 is silenced, leaving GPX4 pathway the sole antioxidation defense mechanism, which makes ferroptosis more inducible when such pathway is targeted. In CML, FRGs are being downregulated. However, the drug-resistant subtype of CML appeared to be more vulnerable to ferroptosis. In this review, the experiments evidence is discussed across these three subtypes. Several compounds are highlighted which have the capability of inducing ferroptosis and the effect of co-administration with existing therapeutic drugs is demonstrated that shows further enhancement in ferroptosis.

Keywords: ferroptosis, leukemia, drug resistance, AML, ALL, CML

1. Introduction

Leukemia is a disease where excess leukocytes are present in blood. This is due to the nature of malignant leukocytes. These leukocytes are highly motile and capable of surviving in circulation like benign leukocytes. But like other cancerous cells, their division is uncontrolled and rapid. Leukemia is a devastating disease that affects many families. Canonical treatments such as chemotherapies are expensive and some patients experience resistance and relapses, decreasing their durable remission. These treatments also tend to pose painful side-effects to patients. Therefore, research is being conducted to investigate the mechanisms of resistance and the development of alternative therapeutic approaches. Current studies on determining the drug resistance mechanism have shown the following findings: Mutations can cause either improved leukemic cell proliferation and survival or change of drug targeting sites; Leukemic cells have higher drug efflux capacity and are quiescent; Bone marrow microenvironment provides adhesion sites and protection for leukemic cells [1].

Ferroptosis is a form of regulated cell death triggered by iron imbalance that differs from classic apoptotic pathway. The sensitivity of ferroptosis is strongly correlated with iron availability. Under normal conditions, extracellular Fe^{3+} (ferric iron) binds to the plasma protein transferrin, then the complex is sequestered by transferrin receptors on cell membrane. Once endocytosed, endosomal

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enzyme STEAP3 reduces Fe^{3+} into Fe^{2+} (ferrous iron), then exits into cytoplasm via Divalent Metal Transporter 1. To store iron, ferritin in the cytosol has ferroxidase domain that oxidizes Fe^{2+} back to Fe^{3+} then packs Fe^{3+} in its core, preventing cell toxicity. Excessive Fe^{2+} is exported from the cell via ferroportin or in exosome. When the balance of iron homeostasis is disrupted, Fe^{2+} accumulates in cytosol and organelles. This promotes Fenton Reaction that generates hydroxyl radical which belongs to Reactive Oxygen Species (ROS). Free radicals enhance activities of ALOX, the lipoxygenase that oxidizes membrane polyunsaturated fatty acids into lipid hydroperoxides and reactive aldehydes. This ruptures the cell membrane bilayer [2]. The ruptured cells release Damage Associated Molecular Patterns that promotes inflammation which further propagate cell death.

Drug resistant leukemic cells exhibit enhanced antioxidative capacity and reduced responsiveness to apoptotic signaling. The unique nature of ferroptosis that it occurs when antioxidative defense fails and lipid peroxidation accumulates via a distinct pathway to induce cell death from organized apoptosis. This has driven the current interest in developing novel treatment strategies targeting drug resistant leukemia.

2. Ferroptosis in the treatment of drug-resistant leukemia

Leukemia is a group of diseases that can be categorized based on two aspects. One is the rapidity of clinical onsets where the disease is either acute or chronic, the other is the disease progression depending on the affected leukocyte lineage whether myeloid or lymphocytic. In this review, the role of ferroptosis as a treatment potential for Acute Myeloid Leukemia (AML), Acute Lymphocytic Leukemia (ALL) and Chronic Myeloid Leukemia (CML) will be discussed.

2.1. AML

Chemotherapy resistance in AML is associated with enhanced nuclear factor erythroid 2-related factor 2 (Nrf2) activity. The study conducted by Liu et al. found that in AML patients, elevated Nrf2 upregulates the expression of Glutathione Peroxidase 4 (GPX4). This is a peroxidase that reduces lipid hydroperoxides using the reduced form of glutathione. Therefore, GPX4 enhances the antioxidative defense in AML leukemic cells, which protects them against ferroptosis. To determine the effect of reduced antioxidation on inducing ferroptosis to improve chemotherapy sensitivity, this study used the inhibitor of Nrf2 (ML385) to treat AML cells (MV4;11) that are synergistically cooperated with GPX4 inhibitors (RSL3 and FIN56) and measured the expression of GPX4 via western blotting. Results have shown that with increased concentration of RSL3 and FIN56, significant decrease in GPX4 expression is shown after 0.5μM and 5μM is applied respectively. It is also found that administrating both ML385 and GPX4 inhibitors has significantly better effect in inhibiting proliferation of different AML cell lines. The impact of such synergistic treatment on ferroptosis was determined by measuring the lipid peroxidation level. Result revealed that combined treatment has significantly better effect in elevating lipid-based ROS accumulation in different AML cell lines. To specify the cause of this accumulation is due to ferroptosis, ferrostatin-1 (Fer-1), a lipid peroxidation blocker by binding lipid radicals. A decrease in cell viability is observed, suggesting cell death occurred. When Fer-1 is applied, the cytotoxicity is restored, suggesting cell death involves production of lipid radicals. Therefore, the dependency of ferroptosis and GPX4 inhibitor treatment is suggested [3].

Drugs targeting the apoptotic pathway by acting on inhibiting the anti-apoptotic protein BCL-2 such as venetoclax may exhibit resistance due to mutations that upregulates other members of BCL-2 family or impairs signaling in apoptosis. The study conducted by Li et al. has found that

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venetoclax-resistant cells have higher gene expression of GPX4 and SLC7A11. But the cells are still sensitive to ferroptosis when exposed to RSL3 APR246 and sorafenib. This correlation also proved using Fer-1 as above [4].

Leukemic cells may also rely on upregulated BET family members proteins, particularly BRD4. This allows increased transcription of survival signaling genes. Therefore, the use of BET inhibitors is common for leukemia treatments. Resistance arises when cells are insensitive to these inhibitors. The study conducted by Zhong et al. has discovered that inhibition of BRD4 down regulates c-Myc, which reduces the expression of Nrf2, therefore, antioxidant defense is weakened, this favors the condition for ferroptosis. This is supported by a reduced cell viability. They have also found that synergistic administration of BRD4 inhibitors and ferroptosis inducers exhibits higher effectiveness [5].

2.2. ALL

Hydnocarpin D (HD) is a compound used in cancer treatment even though the mechanism of action is unknown. To determine its potential effect, Lou et al. investigated multiple aspects of HD using T-cell-ALL cell line. Results have shown that HD can act as a multi-target anti-leukemia compound by activating cytotoxic autophagy, which triggers both apoptosis and ferroptosis. Evidence shows that when ATG autophagy gene family is knocked down, cytotoxic effect of HD has weakened. Together with reduced cell viability, it suggests that autophagy in this case is prone to induce apoptosis, which is also supported by the staining of nuclear content and calculated apoptosis ratio. The trigger of ferroptosis is again proved after the application of Fer-1, HD induced cell death has reduced. Therefore, HD can be a potent drug to be administered if patient experiences resistance towards chemotherapy [6].

Another study conducted by Pontel et al. has shown that targeting ferroptosis to induce cell death is exceptionally effective against ALL subtype, due to the inability of expressing FSP1, a ferroptosis-suppressing protein. In ALL cells, FSP1 gene promoters are hypermethylated, this impairs Nrf2 binding, which leads to impaired activation of FSP1. Therefore, the transcription of FSP1 is silenced. This makes the cell dependent on GPX4 to execute antioxidative defense. Cell viability test is conducted to determine the involvement of cell death. Together with the test of Fer-1, result showed that viability is significantly reduced but with some exceptions, and suggested a potential mixture of cause of cell death including both apoptosis and ferroptosis [7]. Relevant research conducted by Lalonde et al. has supportive evidence that shows ALL cells are more vulnerable to ferroptosis. This study conducted genome wide CRISPR screening to help identify gene vulnerability in B-cell ALL cells. Result has revealed that loss or inhibition of GPX4 trigger cell death in ALL that is not common in other leukemic subtype cells. It is found that FSP1 is poorly expressed in B-ALL cells, which aligns with the previous study mentioned. This causes B-ALL cells to have higher oxidative stress, lower GSH content and lower SLC7A11 expression compared to other leukemic subtypes. Hence, B-ALL cells are highly reliant on GPX4 activity [8]. Together, if such GSH-GPX4 pathway is targeted by inhibiting the synthesis of GPX4 or GSH, ferroptosis is highly effective in eliminating ALL cells.

2.3. CML

Different from the previous two subtypes of leukemia and normal cells, CML has significantly lower ferroptosis capacity. The reduced ability to conduct ferroptosis in CML patients is mostly due to the downregulation of Ferroptosis-related genes (FRG). Zhong et al. has managed to identify five of the

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FRGs that are significantly lower in expression in CML. However, drug-resistant CML cells are more sensitive to ferroptosis. Evidence has shown that resistant cells show higher baseline ROS level as well as increased vulnerability to ferroptosis when erastin is applied. The proof of ferroptosis involvement is again determined using Fer-1 and exhibits reversed effect. Low dose of erastin has shown to have the ability to sensitize resistant cells to imatinib that targets BCR-ABL fusion protein to prevent cell proliferation [9].

The traditional method to induce ferroptosis was to utilize the Nrf2-SLC7A11-GPX4 axis. One way to achieve that is by administrating hyperoside. Wei et al. conducted research and determined that hyperoside induces ferroptosis. Statement is again supported by using Fer-1 observed reversed effect. Apoptosis was also observed via monitoring nuclear staining, but ferroptosis plays the dominant role. Hyperoside physically binds to and reduces Nrf2 mRNA transcript, thereby decreasing expression of its downstream proteins SLC7A11 and GPX4. Hence, redox balance within the cell is disrupted, inducing ferroptosis. This research has also proved that combined administration of hyperoside and imatinib shows reduced CML cell viability which aligns with the study mentioned above [10].

A novel approach to induce ferroptosis was proposed by Zhu et al. The design of Mn-Zn ferrite nanoparticle was used to determine its effect in drug resistance in CML. Both in vivo and in vitro experiments were conducted using adriamycin-resistant K562 cells and mouse models respectively. The main finding states that such nano particles enhance efficacy of adriamycin. Elevated ROS production was shown along with depleted GSH and downregulated GPX4 expression [11]. This evidence suggests disrupted cell redox balance and reduced cell viability showed consistency with ferroptotic cell death, which implies its role. But unlike other studies, Fer-1 was not used to support the hypothesis of ferroptosis involvement, despite ferrite contain iron.

3. Conclusion

Drug resistance in leukemia treatment is the main obstruction of long-term remission. Resistance evokes from multiple reasons, including the mutations in apoptotic pathways, enhanced antioxidative defense, altered metabolic capacity as well as protection from the bone marrow where adhesion provision and local microenvironment alteration favor the survival of leukemic cells. Given this, the studies involving ferroptosis are conducted to determine a way to trigger cell death bypassing apoptotic features. Experiments discussed in this review collectively show evidence that when ferroptosis inducer is being applied, ROS is significantly increased, indicating its therapeutic purposes.

The three leukemia subtypes discussed each has distinct sensitivity and mechanism against ferroptosis. AML shows strong dependence on Nrf2 upregulation, which upregulates the Nrf2–SLC7A11–GPX4 antioxidant axis. Agents that disrupt this pathway, including ML385, RSL3 and FIN56, effectively restore AML susceptibility to ferroptosis. In ALL, silencing of FSP1 significantly weakens antioxidant capacity, making these cells highly reliant on GPX4. Compounds such as HD, which triggers both apoptosis and ferroptosis, as well as GPX4 or SLC7A11 inhibitors like erastin, can efficiently induce ferroptosis. Drug-resistant CML cells display increased ferroptosis vulnerability, different from other CML cells where FRGs are lacking. Treatments such as erastin and hyperoside promote ferroptosis in these cells through similar suppression of the antioxidant pathway.

Most studies in this review used Fer-1 to determine whether ferroptosis was responsible for reduced cell viability. The combined outcome with measurements of ROS accumulation, these methods strengthened the evidence for ferroptosis involvement. Several studies also demonstrated

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that co-administration of ferroptosis inducers, such as APR246, sorafenib, Mn–Zn ferrite nanoparticles, and the compounds mentioned above or with resisted chemotherapeutic agents produced stronger cytotoxic effects than either treatment alone.

Overall, these findings highlight ferroptosis as a promising therapeutic potential across leukemia subtypes. However, further studies should be conducted with trials to determine its clinical significance. Investigating its side effects, delivery methods and other cellular proteins other than Fer-1 can be used as a marker to determine ferroptosis. With further investigation, ferroptosis associated therapeutic approach may ultimately provide more effective treatment option for leukemic patients with drug resistance and restore their disease remission.

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