Transactions on Cancer (2023)
Clausius Scientific Press, Canada

DOI: 10.23977/tranc.2023.040109
ISSN 2523-6482 Vol. 4 Num. 1

Molecular Regulation Mechanisms of Ferroptosis and Its Progress in AML Treatment

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Keywords: Ferroptosis, Acute Myeloid Leukemia, Oxidative-Antioxidative Mechanisms, XCT-GSH-GPX4 Pathway, Autophagy

Abstract: This review focuses on the intricate molecular mechanisms and advancements of ferroptosis in Acute Myeloid Leukemia (AML) treatment. AML, an uncontrolled proliferation of undifferentiated myeloid precursor cells, demonstrates a high degree of chemotherapy resistance, resulting in poor prognosis. Ferroptosis, a distinct form of cell death involving iron accumulation and lipid peroxidation, has emerged as a promising therapeutic strategy. Herein, we dissect the oxidative-antioxidative mechanisms and iron death, highlighting the roles of the glutathione system and Fenton reaction. Furthermore, the association of lipid peroxidation with ferroptosis, as well as the advancements in AML research focusing on the XCT-GSH-GPX4 pathway and the interplay of autophagy and ferroptosis, are detailed. This comprehensive analysis underscores the potential of ferroptosis as a targeted therapeutic approach for AML.

1. Introduction

AML is the predominant malignant myeloid disease in adults, representing a clonal disorder of the hematopoietic system triggered by diverse genetic and epigenetic insults[1]. It is marked by the unrestrained proliferation of immature myeloid precursor cells[2]. Despite the rising incidence rate of AML over the years[3], advancements in traditional chemotherapy regimens have done little to enhance prognosis, with AML often demonstrating considerable chemotherapy resistance, high recurrence rates, and a poor prognosis[4]. This underscores the critical need for novel therapeutic interventions. In 2012, a unique cell death mode was proposed by Dixon et al. [5], distinguished morphologically, biochemically, and genetically from apoptosis, necrosis, and autophagy, and was thus termed 'Ferroptosis.' Upon examination through transmission electron microscopy, that cells undergoing ferroptosis reveal unaltered nuclear size without substantial changes and absence of chromatin condensation. However, observable traits include mitochondrial shrinkage, increased mitochondrial membrane density, reduction or vanishing of cristae, and the rupture of the mitochondrial outer membrane [5]. Key biochemical markers of ferroptosis encompass the buildup of iron ions, clustering of reactive oxygen species (ROS), and lipid peroxidation resulting in

oxidative damage to the cellular membrane.

2. Molecular mechanism of ferroptosis

The induction of ferroptosis is also strongly associated with an imbalance between oxidation and anti-oxidation.

2.1 Oxidative-antioxidative mechanisms and ferroptosis

Oxidative damage is caused by an imbalance between the body's production of free radicals and its antioxidant systems, which include the glutathione (GSH) system, the Q10 system, and the tetrahydrobiopterin coenzyme system. Among these, the GSH system plays a primary role in antioxidant actions[6]. Glutathione is an active tripeptide composed of glutamic acid, cysteine, and glycine, and it's a significant antioxidant within the body. Glutathione exists in two forms: the oxidized form (GSSG) and the reduced form (GSH). These participate in regulating the balance of oxidation-antioxidation within cells. The rate-limiting substrate for GSH synthesis is cysteine, but cysteine is extremely unstable in the body, and extracellular cysteine exists as oxidized cystine. The primary route of cystine entering the cell is mediated by the cell surface cystine/glutamate antiporter (System Xc−). This transporter is composed mainly of the light chain solute carrier family 7 member 11 (SLC7A11, XCT) and the heavy chain solute carrier as family 3 member 2 (SLC3A2). Among them, the subunit playing the main role is SLC7A11, which is responsible for the transmembrane exchange of cystine and glutamate[7]. After cystine enters the cell, it is oxidized into cysteine. Then, under the action of glutamate-cysteine ligase and glutathione synthetase, it combines with glycine to generate GSH. Glutathione peroxidase 4 (GPX4) is a unique enzyme that can reduce peroxidized polyunsaturated fatty acid-containing phospholipids (PUFA-PLs) into their corresponding alcohols through the cofactor GSH. By eliminating lipid peroxides, it can inhibit the occurrence of ferroptosis in cells[8].

2.2 Iron ion accumulation and ferroptosis

Excessive accumulation of intracellular Fe^{2+} can cause cell ferroptosis through the Fenton reaction. Relative to normal cells, tumor cells indeed show stronger dependence on iron in the environment[9-10]. Studies have found that extracellular Fe^{3+} enters cells through transferrin receptor 1 (TFR1) on the cell membrane. Once Fe^{3+} enters the cytoplasm, it is reduced to Fe^{2+} and transported to the unstable iron pool in the cytoplasm. If the intracellular iron cannot be utilized in time, it is stored in ferritin, the primary intracellular iron storage protein complex, composed of ferritin light chain polypeptide 1 (FTL1) and ferritin heavy polypeptide 1 (FTH1) [11]. When the body's demand for iron increases, Fe^{2+} is excreted through the solute carrier family 40 member 1 (SLC40A1) in the cell membrane [12]. It can also be excreted in the form of ferritin via exosomes. In metabolic processes, an imbalance among iron intake, storage, and efflux may lead to excessive accumulation of iron ions, thereby causing cell ferroptosis via the Fenton reaction. The Fenton reaction refers to the reaction in which Fe^{2+} and hydrogen peroxide(H_2O_2) generate Fe^{3+} and oxygen radicals. When there is an excess of iron in cells, oxygen radicals and reactive oxygen species can be produced via the Fenton reaction, activating iron-containing enzymes such as lipoxygenases. This leads to the generation of oxidative stress and lipid peroxidation, which in turn induces ferroptosis [13].

2.3 Lipid Peroxidation and Ferroptosis

The massive accumulation of lipid peroxides is also a characteristic of ferroptosis. In cells, polyunsaturated fatty acids (PUFAs) are synthesized into PUFA-CoA under the action of acyl-CoA synthetase long-chain family member 4 (ACSL4). Subsequently, lysophospholipid acyltransferase 3 (LPCAT3) promotes PUFA-CoA esterification to generate PUFA-PLs[14]. NADPH is oxidized under the action of NADPH oxidase (NOX) to produce NADP+ and H_2O_2. H_2O_2 and Fe^{2+} generate oxygen radicals and ROS through the Fenton reaction. ROS can be integrated into cell membrane phospholipids, causing PUFAs to undergo peroxidation. An abundance of peroxidized PUFA-PLs is produced through enzyme-mediated reactions driven by lipoxygenases and non-enzyme-mediated oxidation reactions driven by the Fenton reaction [15]. This eventually leads to the destruction of the phospholipid bilayer, triggering ferroptosis.

3. Progress in Research on Ferroptosis in AML

In recent years, the resistance rate to traditional therapies for acute myeloid leukemia (AML) has been increasingly high, and the therapeutic efficacy has progressively diminished. Studies have revealed that various drugs can induce ferroptosis in AML cells and effectively target and kill these cells in vivo. Thus, ferroptosis could potentially emerge as a new direction for the treatment of AML.

3.1 The XCT-GSH-GPX4 Pathway and Ferroptosis in AML Cells

The GSH-GPX4 antioxidant system plays a crucial role in the process of ferroptosis. Inhibition of the GSH-GPX4 system can lead to ROS accumulation, thereby triggering ferroptosis in AML cells. Studies have shown that early exposure to APR-246 in AML cell lines such as HL-60, SET2, and THP1 can induce ferroptosis in AML cells, regardless of the TP53 mutation status. This ferroptosis can be inhibited by iron chelator deferoxamine (DFO), lipophilic antioxidant Ferrostatin-1 (Fer-1), and lipid peroxidation inhibitors and is related to the accumulation of ROS. The inhibition of GPX4 through inhibitors such as RSL3 and FINO2, the knockout of GPX4, and the inactivation of the SLC7A11 gene all have a synergistic anti-leukemic effect with APR-246[16].

3.2 Autophagy and Ferroptosis in AML Cells

Autophagy is the process of self-degradation in cells, used to degrade and eliminate abnormal proteins and damaged organelles to maintain cellular metabolism and dynamic balance[17]. The AMPK/mTOR signaling pathway is an essential part of cell autophagy. AMPK as an upstream factor can effectively promote cell autophagy, and mTOR, the downstream factor of AMPK, can antagonize the promoting effect of AMPK on autophagy. Phosphorylated AMPK (p-AMPK) can trigger an autophagy cascade, increasing LC3-II, Beclin1 expression, inhibiting p62, and mTOR protein expression, thereby promoting autophagy. When phosphorylated, mTOR forms p-mTOR, which significantly inhibits cell autophagy[18]. Studies have found that Dihydroartemisinin (DHA) can regulate the activity of the AMPK/mTOR/70pS6K signaling pathway by inducing mitochondrial dysfunction and ROS accumulation, causing cell autophagy and leading to ferroptosis in AML cells. Both in vitro and in vivo, DHA can preferentially target AML cells, suggesting that DHA may become a promising targeted drug for the treatment of AML[19][20]. Typhneoside (TYP) can also induce AML cell ferroptosis dependent on autophagy-mediated ferritin degradation through the AMPK/mTOR signaling pathway, and therefore, TYP can serve as a potential anti-AML drug[20].

4. Conclusion and Prospects

Ferroptosis, as a novel form of cell death, offers new approaches and targets for the treatment of AML, presenting a new opportunity for AML treatment. The substantial decrease in normal cells in patients after AML chemotherapy leads to a significant reduction in the patient's resistance, making it valuable to conduct more in-depth research on how to induce specific ferroptosis in AML cells. Secondly, drug resistance is common in AML cells. Whether the synergistic anti-AML effect of ferroptosis and chemotherapeutic drugs can alleviate resistance while ensuring the elimination of tumor cells is an important future research direction. Lastly, whether the active ingredients of natural herbal medicines can serve as new drugs to target AML through the pathway of ferroptosis deserves further exploration. However, current research on AML ferroptosis is scarce. Deeper investigations into the relationship between AML and ferroptosis could contribute to providing new directions for AML treatment.

Acknowledgements

The authors gratefully acknowledge the financial support from Shaanxi University of Chinese Medicine Research Program (No. 2020CX58), Shaanxi Provincial Administration of Chinese Medicine Middle and Young Science and Technology Backbone Program (No. 2023-ZQNG-006), Shaanxi Provincial Health Commission Research Program (No. 2016D030, 2018D087), The Second Affiliated Hospital of Shaanxi University of Chinese Medicine Research Program (No. 2021YB02).

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