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Research Progress on the Mechanism and Treatment of Ferroptosis in Brain Glioma

Xiaohui Han[1, 2], Shihua Liu[1, 3], Sen Yang[1, 4], Aixia Sui[1, *]

[1]Department of Oncology, Hebei General Hospital, Shijiazhuang, China

[2]Graduate School, Hebei Medical University, Shijiazhuang, China

[3]Graduate School, Hebei North University, Zhangjiakou, China

[4]Graduate School, North China University of Science and Technology, Tangshan, China

Email address:

suiaxhebei@126.com (Aixia Sui), 1577280718@qq.com (Xiaohui Han), lsh18732548669@163.com (Shihua Liu), yang_961110@163.com (Sen Yang)

[*]Corresponding author

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Abstract: Ferroptosis is a new type of programmed cell death discovered in recent years. It is a regulatory cell death induced by iron dependent lipid peroxide injury. Ferroptosis plays a critical role in the development of glioma, affecting tumor proliferation, angiogenesis, tumor cell necrosis, and the formation of an immune-resistant tumor microenvironment. Glioma is the most common intracranial malignant tumor, with the characteristics of high incidence rate, high recurrence rate, high mortality rate and low cure rate. At present, the main standard treatment plan is tumor surgical resection, synchronous radiotherapy and chemotherapy, etc. Because of the extremely low 5-year survival rate and high recurrence rate of glioma patients, new effective treatment strategies are expected. With the extensive study of regulatory cell death in malignant tumors, there is increasing evidence that iron death is closely related to the development and outcome of glioma. Inducing iron death becomes an attractive strategy for glioma treatment. In this paper, we summarize the research on this aspect and summarize it in gelatin. The mechanism of action and therapeutic research value of tumor are expected to develop new therapeutic strategies and provide a certain theoretical basis for the in-depth research in this field.

Keywords: Ferroptosis, Glioma, Therapeutic Target, Molecular Mechanism

1. Introduction

Glioma is the most common primary malignant tumor of adult central nervous system, accounting for about 50%-60% of central nervous system (CNS) tumors [1] and about 81% of intracranial malignant tumors [2, 3]. On the basis of the latest classification criteria of WHO [4], the pathological types of gliomas can be divided into low-grade gliomas (LGG, Grade 1-2) and high-grade gliomas (HGG, grade 3-4). WHO Grade 4 glioblastoma (GBM) has the worst prognosis due to its high proliferation rate, tumor cell heterogeneity, diffusion and invasion, which make glioma difficult to be completely resectable [5]. Current clinical treatments for glioma include surgical resection, radiotherapy, chemotherapy, novel molecular targeted therapy and immunotherapy [6], etc., but all fail to bring ideal curative effect, and the overall prognosis is extremely poor [7, 8]. In recent years, it has been found that the development of glioma can be controlled to a certain extent by inducing iron death of glioma cells.

Cell death includes regulatory cell death (RCD) and accidental cell death (ACD). RCD is an active and orderly way of cell death determined by genes. Programmed cell death (PCD) is a mechanism for life maintenance activities in the body. The term "ferroptosis" was first proposed by Dixon et al in 2012 [9], and iron death was officially included in RCD by the Committee on Cell Death Nomology in 2018 [10]. Ferroptosis is a new type of programmed cell death, and its main molecular mechanism is reactive oxygen species (ROS) and irresistible iron-dependent accumulation of lipid peroxidation leading to cell death [11]. Studies have shown

that ferroptosis is not only involved in the mechanism of TMZ resistance, but also in glioma sensitization. In conclusion, this paper reviews the mechanism and treatment of iron death in glioma.

2. Mechanisms Related to Ferroptosis

2.1. Cystine/Glutamate Reverse Transport System and Ferroptosis

Ferroptosis was first proposed by Dixon et al in 2012 [9]. Ferroptosis is mainly characterized by cell death caused by the increase of free ferrous ions in cells and the excess of lipid reactive oxygen species caused by the reduction of membrane lipid polyunsaturated fatty acid peroxidation and glutathione peroxidase 4 synthesis [12]. Ferroptosis can be induced by exogenous and endogenous pathways, which are achieved by inhibiting cell membrane transporters including system xc- or activating serotransferrin and lactotransferrin. The endogenous pathway is to block the activation of intracellular antioxidant enzymes [e.g. glutathione peroxidase 4 (GPX4)].

Cystine-glutamic acid reverse transport system (system xc-) is a heterodimer composed of SLC7A11, a member of the solute carrier family, and SLC3A2, a member of the solute carrier family. The inhibitory activity of the Xc system leads to decreased GPX4 activity, ROS accumulation, lipid oxidative stress, and cell iron death. Glutathione peroxidase 4 (GPX4) has the function of scavenging lipid peroxides. The inactivation of GPX4 can break the oxidation balance, leading to the destruction of lipid peroxides membrane structure and the activation of ferroptosis [13-14]. Therefore, GPX4 is the only enzyme that reduces membrane lipid peroxide (LOOH) to non-toxic lipid alcohol (LOH) by consuming reduced glutathione. Because GPX4 primarily utilizes the antioxidant glutathione to reduce lipid hydrogen peroxide, its activity is largely dependent on the level of glutathione within the cell. Inhibition of GPX4 activity leads to excessive lipid peroxidation and subsequent cell iron death.

2.2. Regulation of Iron Metabolism

The essence of ferroptosis is iron metabolism disorder and lipid peroxidation, and its core molecular mechanism is oxidative damage and the imbalance of antioxidant system.

Iron homeostasis is precisely regulated by iron regulatory protein (IRP2) and iron response elements. Reduced IRP2 activity and increased expression of transferrin (Tf) and transferrin receptor (TFR) can lead to imbalance of iron homeostasis and abnormal increase of unstable iron in cells, which is a key factor affecting ferroptosis [15]. Another source of free iron is ferritin heavy chain 1 (FTH1). FTH1 is recognized by the specific nuclear receptor coactivator 4 (NCOA4) to form a complex. This complex fuses with the lysosome, and ferritin is degraded and free iron is released [16]. Studies have shown that lysosomes are necessary to activate iron death. NCOA promotes iron death in some cell lines and is required for Erastin-induced ferritin degradation, free iron accumulation and lipid peroxidation [17].

2.3. The Regulation of the Lipid Peroxidation

One of the characteristics of ferroptosis is the accumulation of lethal reactive oxygen species caused by peroxidation of polyunsaturated fatty acids (PUFA), mainly including superoxides, hydroxyl radicals, hydrogen peroxide and lipid peroxides [18]. Long-chain lipoacyl-coA synthetase 4 (ACSL4) and lysophosphatidyllecithin acyltransferase 3 (LPCAT3) are key enzymes that regulate PUFA synthesis and remodeling in phospholipid membranes [19]. Inhibition or lack of it can enhance cell resistance to ferroptosis. The organelles membrane containing polyunsaturated fatty acid (PUFA), especially arachidonic acid (AA) and adrenic acid, AdA) -Phosphatidylethanolamine (PE) membrane is highly vulnerable to oxidative attack [20]. ACSL4 catalyzes AA to produce arachidonic acidyl coA, which is then esterified to AA-PE under the action of LPCAT3, and finally Aa-PE is oxidized to lipid peroxide by arachidonic lipoxygenase [14]. PUFA oxidation damages the structure and fluidity of the plasma membrane by changing the lipid bilayer structure and geometry, and oxidized lipid clusters in the membrane damage its barrier function by forming hydrophilic pores [21].

Lipid peroxidation can occur in the following two ways: non-enzymatic and enzymatic lipid peroxidation cascades. Excess iron triggers a non-enzymatic lipid peroxidation cascade, the Fe^{2+} dependent Fenton reaction, which oxidizes Fe^{2+} to Fe^{3+} by reacting with hydrogen peroxide, resulting in the production of highly reactive hydroxyl radicals, which are the most active oxygen species. Under normal conditions, iron is mainly stored as ferritin and hemosiderin, with only a small amount of free Fe^{2+} as the iron source of the Fenton reaction. The enzymatic reaction is mainly through the oxidation of free PUFA and phosphatidyl ethanolamine (PE), phosphatidyl choline and cardiolipin containing PUFA, in which PE is more easily oxidized than phosphatidyl choline [22]. Lipid hydroperoxides (LOOHs) production lipid hydroperoxides (loohs) by lipoxygenase, LOX), catalytic function of reduced nicotinamide adenine dinucleotide phosphate oxidase (Nox), cyclooxyoxidase and cytochrome p450s [23]. It has been reported that PE binding protein 1 (recombinant recombinant hatidylethanolamine Binding Protein 1) induces iron death through specific binding to LOX15 [24]. Although the downstream molecular actor in the ferroptosis pathway is unknown, the accumulation of LOOHs and the production of its downstream products malondialdehyde and 4-hydroxy-2-nonenal have been identified as markers of ferroptosis [25].

2.4. GPX 4 Was Associated with Ferroptosis

GPX4 is a key enzyme in the hydrolysis of lipid peroxides in vivo, which can directly reduce phospholipid peroxide to hydroxylphospholipid, maintain the balance of intracellular free radical content, and is a key regulatory factor for ferroptosis [9]. GPX4 relies on the cofactor glutathione (GSH) to reduce toxic lipid peroxides to non-toxic lipid alcohols, repair damaged biofilms and prevent the occurrence of iron death. Extracellular cysteine is mainly actively ingested by

cells through System Xc- for GSH synthesis, and the trans-vulcanization pathway can also supplement GSH levels. The System Xc- system consists of two subunits, SLC7A11 and SLC3A2, and the deletion of SLC7A11 or GPX4 gene can lead to lipid peroxidation and ferroptosis in some cells or tissues [26].

3. The Mechanism and Therapeutic Value of Ferroptosis in Glioma

Tumor metabolism is different from normal cell metabolism. In order to obtain more energy, tumor cells will undergo metabolic reprogramming, which is called Warburg effect [27]. The presence of high levels of ROS and PUFAs expression and strong iron dependence in gliomas provides a new direction for the treatment of gliomas.

The damage-associated molecular pattern (DAMP) of iron death is more specific than other forms of cell death. On the one hand, ferroptosis can recruit and activate a large number of immune cells at the tumor site in vitro and promote the maturation of dendritic cells [28, 29]. Ferroptosis inducers can be used as sensitizers for anti-tumor immunotherapy [30-32]. Studies have shown that ferroptosis combined with radiotherapy and chemotherapy can overcome part of drug resistance, inhibit glioma growth and prolong survival time [31, 33, 34]. On the other hand, ferroptosis is a unique form of autophagy [35] and leads to iron accumulation, which is not only related to iron uptake and the formation of new blood vessels during tumor growth [36], but also an important factor in the construction of immunosuppressive glioma microenvironment, such as regulating the proliferation of B cells and T cells and the immunophenotypic differentiation of tumor-associated macrophages [37].

It was found that glioma cells had lower expression of ACSL4 compared with normal brain cells. Knockouting ACSL4 gene can significantly improve the viability of glioma cells [18]. The results showed that neutrophils extensively infiltrated the necrotic areas of tumors and increased with tumor progression, and the degree of glioma tumor-associated neutrophils infiltration was positively correlated with the degree of tumor necrosis [38]. Studies have shown that neutrophils are involved in promoting tumor necrosis by triggering ferroptosis in tumor cells. Studies have shown that the ferroptosis inducer Sorafenib combined with radiotherapy plays a synergistic role in killing glioma cells [34]. Doranidazole can increase the level of metal reductase STEAP3 and NADH, which can be used as sensitizer to counteract radiotherapy resistance, produce cytotoxicity, limit the growth of glioma cells, and significantly prolong the survival [30].

The oral alkylating agent temozolomide (TMZ) is a first-line chemotherapy agent for the treatment of glioma. It can prolong the survival time of glioma patients to a certain extent. However, due to its drug resistance, only some patients can benefit from TMZ chemotherapy [39]. The combination of the ferroptosis inducer erastin and TMZ has been reported to enhance TMZ sensitivity in a number of ways [31]. In vitro use of hydroxychloroquine (HCQ) and its derivative Anacaine (QN) can penetrate the blood-brain barrier and impair TMZ-induced autophagy, thereby inducing ferroptosis and increasing TMZ sensitivity [40]. Dihydroartemisinin (DHA) has been shown to enhance iron death by producing ROS and inhibiting GPX4 initiation, thereby exerting anticancer activity [41]. Aminoflavone (AF) is a polyphenol that is widely found in cypress trees and has anti-inflammatory and antitumor effects. Studies have shown that AF can trigger glioma ferroptosis in an autophagy dependent manner, thus playing an antitumor role [42]. Accumulation of reactive oxygen species and LPO was observed in glioma cells treated with curcumin analogue ALZ003. In vitro and animal studies have shown that ALZ003 inhibits the growth of TMZ-resistant gliomas by acting on GPX4, a key molecule in the iron death pathway, without cytotoxic effects on normal astroglioma cells [32].

In addition, because of the close relationship between ferroptosis and lipid metabolism, many glioma drugs can exert therapeutic effects through LPO-mediated cell iron death. Brucine, an indole alkaloid extracted from brucine seeds, can promote LPO, lead to ferroptosis of glioma cells, and ultimately inhibit the development of glioma cells in vitro and in vivo [43]. Non-steroidal anti-inflammatory drugs (NSAIDs) induce iron death in glioma cells, which is associated with abnormal increase of intracellular LPO [44]. Studies have shown that gallic acid (GA) can effectively reduce Fe^{3+} to Fe^{2+} and can induce iron death of GBM cells as a substrate of continuous Fenton reaction [45, 46]. Zhang et al. designed a GA-based targeted nano drug that combines ferroptosis with photothermal therapy to treat glioma [46].

Ferroptosis and ncRNA are closely related to tumor [47]. Among ncRNAs, miRNAs, lncRNAs, and circRNAs are all involved in the potential regulatory mechanism of tumor ferroptosis [48]. NcRNAs can regulate protein levels of ferroptosis related genes [49], affect mRNA expression of ferroptosis related genes [50], lead to modification of m6A and control epigenetic activity [51].

4. Conclusion

Ferroptosis is a new pattern of programmed cell death, which is different from other RCDS and is the result of accumulation of iron-dependent lipid peroxidation. It plays a critical role in the development of glioma by influencing the proliferation, invasion, tumor necrosis and angiogenesis of glioma cells, and participating in the construction of immunosuppressive glioma microenvironment. Existing studies have shown that ferroptosis inducers combined with radiotherapy or TMZ can improve the therapeutic resistance of glioma, and many drugs based on iron death can play a positive role in the treatment of glioma. Of course, laboratory to clinical application needs to be through the analysis of tumor tissue samples, analysis of the key factors of ferroptosis gene expression, clinical trials and a series of studies mature. According to the current research results, it is a meaningful

and feasible direction to treat glioma by inducing ferroptosis. For the sake of further apply ferroptosis to glioma treatment, we need to further investigate the mechanism involved in ferroptosis.

Competing Interests

The authors declare that they have no competing interests.

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