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Progress of ferroptosis in gastrointestinal tumors

Zhang Chanchan[1], Sun Jianfei[2,*], Guo Hui[2], Si Mingming[2]

[1]Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712000, China
[2]The First Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712000, China
[*]Corresponding author: 575854654@qq.com

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Abstract: Ferroptosis is a new method of programmed cell death, which is different from other cell death. It is characterized by cytoplasmic membrane blistering, chromatin condensation, mitochondrial shrinkage, volume reduction, membrane density increase, cristae reduction or disappearance, mitochondrial outer membrane rupture, and nuclear membrane integrity. It plays an important role in the treatment of tumors, especially in gastrointestinal tumors, and has potential research potential. This article will review the mechanism of ferroptosis and its related reports on gastrointestinal tumors in recent years.

1. Introduction

Gastrointestinal tumors are the most common cause of cancer-related deaths worldwide, accounting for about half of all cancers and seriously affecting human health. Recently, ferroptosis plays an important role in the treatment of gastrointestinal cancer. It is a new way to induce cell death in cell process, which is of great significance to clinical research. This article summarizes the related mechanisms of ferroptosis and its research reports on gastrointestinal tumors in recent years.

2. Ferroptosis

Ferroptosis is a new form of programmed cell death. In 2012, Dixon [1] et al. named Erastin-induced ferroptosis a novel biochemical cell death mode with unique genetic characteristics. Prior to this, Dolma [2] et al. found that Erastin could induce the death of tumor cells with RAS oncogene mutations, while YANG [3] et al. suggested that the use of inhibitors related to apoptosis and necrosis processes could not change the cell death caused by Erastin, but iron chelators and antioxidants could control this cell death pattern. When ferroptosis occurs, the cell 's cytoplasmic membrane blisters, chromatin condensation, mitochondrial shrinkage, volume reduction, increased membrane density, ridge reduction or disappearance, mitochondrial outer membrane rupture, nuclear membrane integrity, these cell morphological changes are different from apoptosis and necrosis [1]. At present, scientific research has confirmed that ferroptosis is mainly caused by the imbalance between lipid ROS involvement and detoxification in cells [4]. When the antioxidant capacity of cells is weakened, the accumulation of lipid ROS (reactive oxygen species) can lead to oxidative stress-induced cell death, that is, ferroptosis.

The occurrence of ferroptosis is mainly regulated by three mechanisms: iron metabolism, lipid

metabolism, and glutathione metabolism. The dysregulation of these three regulatory pathways ultimately significantly reduced GPX4 (glutathione peroxidase 4) activity and increased intracellular lipid ROS levels, which resulted in decreased cellular antioxidants, increased lipid ROS, oxidative damage to cell membranes, and ferroptosis. FSP1 (ferroptosis inhibitor protein 1) can induce lipid peroxidation and ferroptosis by directly eliminating lipid ROS independent of GPX4 [5].

2.1 Iron metabolism

A large number of studies have found that Fe^{3+} produced by Fe^{2+} and lipid peroxides enters the cell through the transferrin receptor (TFRC) and is transported to an unstable iron pool, which is reduced to Fe^{2+} under the action of NCOA4 (nuclear receptor coactivator 4). Fe^{2+} is also an important factor affecting lipid peroxidation and ferroptosis. Secondly, dietary iron enters the cell and reacts with H2O2 to trigger Fenton reaction [6]. A large amount of ROS produced cannot be effectively eliminated, which will lead to the oxidation of DNA cell membrane and protein, resulting in ferroptosis. Therefore, the absorption, distribution, metabolism, transformation and excretion of iron ions are closely related to ferroptosis. Enriching exogenous iron ions without supplementing other divalent metal ions can accelerate Erastin-induced ferroptosis [1]. Studies have shown that [3], knocking out the cell surface transferrin receptor can prevent iron overload in cells, or increase the amount of iron stored in the inert pool by increasing cytoplasmic ferritin, thereby preventing ferroptosis. By knocking out SLC40A1 (Solute carrier family 40 member 1), blocking intracellular iron output will accelerate Erastin-induced ferroptosis in neuroblastoma [7].

2.2. Lipid metabolism

The accumulation of lipid peroxides in cells is an important part of ferroptosis. Lipid peroxidation pathway is divided into enzymatic lipid peroxidation and non-enzymatic lipid peroxidation. The non-enzymatic reaction is the Fe^{2+}-dependent Fenton reaction, which reduces Fe^{2+} to Fe^{3+} by reacting with H2O2 to produce highly reactive hydroxyl radicals, which is the most active active oxygen [8]. The enzymatic reaction is to oxidize free PUFA and PE containing PUFA, phosphatidylcholine and cardiolipin, in which PE is more easily oxidized than phosphatidylcholine [9]. Free PUFAs produce prostaglandins under the action of COXs (cyclooxygenases), and produce lipid hydroperoxides under the action of LOXs (lipoxygenases). LOXs are iron-containing proteins that catalyze the peroxidation of PIFA on the cell membrane and induce cell ferroptosis [10]. The catalytic oxidation of POR also depends on the electron transfer of Fe^{2+}, suggesting that iron affects cell death not only through iron metabolism, but also through lipid metabolism. [11] In addition, in the non-enzymatic oxidation process initiated by PUFAs and ROS, ROS is decomposed into stable non-free radical products by antioxidants, thereby inhibiting the occurrence of ferroptosis.

2.3 Glutathione (GSH) metabolism

System XC − (glutamate-cystine antiport system) is a cystine transporter protein on the surface of cell membrane, which is composed of light chain SLC7A11 (solute carrier family 7 member 11) and heavy chain SLC3A2 (solute carrier family 3 member 2). It participates in the exchange of intracellular glutamate and extracellular cystine, and synthesizes GSH to regulate ferroptosis [12]. When System XC − is selectively inhibited, the body reduces the absorption of cystine, and the synthesis of GSH is reduced, resulting in the accumulation of lipid peroxides [13]. In addition, since GPX4 is a key enzyme in the antioxidant system, it can reduce toxic phospholipid hydroperoxides to non-toxic phospholipid alcohols, and GSH will affect the activity of GPX4.Therefore, the reduction of GPX4 can increase phospholipid peroxides, thereby promoting lipoxygenase-mediated lipid

peroxidation and promoting the occurrence of ferroptosis. In addition, P53 promotes ferroptosis by inhibiting SLC7A11 transcription, reducing GSH production, inhibiting GPX4 activity, and promoting ferroptosis.

3. Effect of ferroptosis on gastrointestinal tumors

3.1 Gastric cancer

Gastric cancer (GC) is the fifth most common malignant tumor in the world and the third leading cause of cancer-related death [14]. Risk factors for gastric cancer include Helicobacter pylori infection, age, smoking, drinking and unhealthy diet [15]. GC patients are mostly treated with surgery. However, the high cost of treatment and the unguaranteed postoperative survival are great challenges for patients. At present, the mechanism of the occurrence and development of gastric cancer is not clear. Further understanding of the pathogenesis of gastric cancer will help to identify new targets for drug action and propose new clinical treatment options. Studies have found that ferroptosis plays an important role in the carcinogenesis and progression of gastric cancer [16].

MiRNA regulates the ferroptosis process of GC cells. Fibroblasts (CAFs) have the characteristics of secreting exosomal miR-522, blocking ALOX15 and lipid peroxidation accumulation to inhibit ferroptosis [17]. It has been found that the circ-0008035 / miR-599 / EIF4A1 axis can accelerate the proliferation of gastric cancer cells and inhibit apoptosis and ferroptosis [18]. C-Myb regulates CDO1 (cysteine dioxygenase 1) and inhibits erastin-induced ferroptosis in gastric cancer cells by up-regulating GPX4 expression [19]. [20] et al. confirmed that Physcion 8-O-β-glucopyranoside induces ferroptosis in gastric cancer cells by regulating the miR-103a-3p / GLS2 axis. MiR-375 attenuates the stemness of GC cells by triggering SLC7A11-dependent ferroptosis [21]. In recent years, LTBP2 has been shown to have therapeutic effects in a variety of malignant tumors. It can significantly inhibit the proliferation of GC cells and reduce the level of GSH in cells, reduce GPX4 activity, increase ROS production and malondialdehyde (MDA) levels, and ultimately lead to GC cell ferroptosis [22]. In addition, inhibition of LTBP2 (β-binding proteins) can regulate the p62-Keap1-Nrf2 pathway, thereby down-regulating GPX4 and xCT expression and up-regulating PTGS2 and 4HNE expression. Propofol, as an anesthetic drug, can induce ferroptosis and inhibit the malignant phenotype of gastric cancer cells by regulating the miR-125b-5p / STAT3 axis [23].

As ferroptosis has attracted more and more attention, ferroptosis inducers have gradually become the research object of many scholars. [24] et al. Identified HC-056456 as an anti-gastric cancer agent by drug reuse strategy, which caused ferroptosis in vitro and in vivo. The 6-TG (6-Thioguanine) selected by the team in the biological activity of 4890 was identified as a potential ferroptosis inducer, which inhibits GSH production, down-regulates GPX4 expression, blocks System XC−, promotes lipid ROS accumulation, and ultimately triggers Fe^{2+} -mediated ferroptosis in MGC-803 and AGS cell lines [25]. As a new JDA (Ji yuan oridonin A) derivative, a2 has the effect of inhibiting the growth of gastric cancer cells. For the first time, a2 was found to induce ferroptosis by inhibiting GPX4 expression and promoting Fe^{2+} level, which is also the main mechanism of a2 inhibiting gastric cancer activity [26]. [27] et al. confirmed that SPIONs induced ferroptosis of GCSCs (Gastric cancer stem cells) by weakening the expression of Xc- / GPX4 axis and 5-hydroxymethylcytidine modification of mRNA in the pathway, so as to achieve its therapeutic effect on gastric cancer.

With the vigorous development of traditional Chinese medicine, the role of traditional Chinese medicine-induced ferroptosis in the treatment of gastric cancer has gradually been noticed. Ophiopogonin [28] induces ferroptosis in gastric cancer cells by blocking the GPX4 / xCT system. Song [29] confirmed that Yiqi Huayu Decoction induced GC ferroptosis by affecting the expression of JAK2-STAT3 pathway and ACSL4. Tanshinone IIA is a substance extracted from the traditional Chinese herbal medicine Salvia miltiorrhiza, which can up-regulate p53 content and induce

ferroptosis in gastric cancer cells [30]. Yiwei Huoxue Decoction induces ferroptosis and ER stress in MC cells and reduces GPX4 / GSH, thereby treating precancerous lesions of gastric cancer [31]. The resistance to cisplatin (DDP) is a common problem in the successful chemotherapy of advanced gastric cancer. ATF3 may induce ferroptosis by blocking Nrf2 / Keap1 / xCT signal transduction, thereby improving the sensitivity of GC cells to cisplatin, reducing drug resistance, and achieving therapeutic effects [32]

3.2 Colorectal cancer

Colorectal cancer (CRC) is one of the most common malignant tumors, ranking fourth in the world. Recurrence and metastasis are important factors for CRC death. The effective treatment of advanced CRC is limited, so it is particularly important to study the new therapeutic mechanism of colorectal cancer.

Ferroptosis-related genes are closely related to the treatment and prognosis of CRC. By analyzing the expression and clinical characteristics of lncRNA in TCGA-COAD and GEO databases, three differentially expressed ferroptosis-related lncRNAs (XXbac-B476C20.9, TP73-AS1 and SNHG15) were identified as biomarkers to establish a prognostic model of CC patients [33] and complete the treatment system. Han et al. [34] explored the transcriptome profile of lncRNA in primary CRC tissues and corresponding paired adjacent non-tumor tissues by RNA-seq, and found that LINC00239 was significantly overexpressed in colorectal cancer tissues. The abnormal high expression of LINC00239 often indicates poor survival and prognosis of colorectal cancer patients. Therefore, ferroptosis induction is a promising treatment strategy for CRC patients with low expression of LINC00239.

The discovery of ferroptosis-related factors provides more options for the treatment of CRC. Tagitinin C is a new ferroptosis inducer, which induces ferroptosis by ER stress-mediated PERK-Nrf2-HO-1 signaling pathway activation [35]. The expression of TIGAR in CRC tissues was significantly higher than that in adjacent normal tissues. Knockout of TIGAR resulted in a significant increase in erastin-induced ferroptosis in SW620 and HCT116 cells, indicating that TIGAR induced ferroptosis resistance in CRC cells through ROS / AMPK / SCD1 signaling pathway [36]. [37] et al. found that knockout of SLC7A11 can increase ROS levels, reduce the levels of cysteine and glutathione, thereby weakening the activity of colorectal CSC and inhibiting the proliferation of CRC. During the induction of environmental factors, the transcription and methylation levels of SLC2A1 are increased, autophagy and ferroptosis are inhibited, and the immune system is defective, resulting in poor prognosis in CRC patients. These results suggest that autophagy and ferroptosis-related gene SLC2A1 is involved in the tumor immune regulation of colon cancer, and SLC2A1 may become a new therapeutic target for colon cancer. HSPA5 inhibits ferroptosis by maintaining the stability of GPX4 to promote the development of colorectal cancer. Although the interaction between HSPA5 and GPX4 cannot completely reverse the decrease of GPX4 induced by erastin, HSPA5 slows down the degradation process of GPX4 and gives CRC cells more time to adapt to the toxicity of erastin, providing potential diagnostic and therapeutic targets for CRC patients [38].

A large number of traditional Chinese medicine extracts are widely used in the treatment of cancer. Curcumin can induce ferroptosis and inhibit the growth of colorectal cancer cells by inhibiting the PI3K / Akt / mTOR signaling pathway. Treatment of HCT-8 cells with curcumin significantly down-regulated GSH, SLC7A11 and GPX4, and significantly increased the levels of iron, MDA and ROS [39]. Andrographis paniculata and OPCs synergistically activate metabolic pathways and enhance ferroptosis to enhance the tumor inhibition of CRC [40]. In addition, some scholars have proposed [41] that Andrographis paniculata achieves the therapeutic purpose of CRC by promoting ferroptosis and inhibiting the β-catenin / Wnt signaling pathway. Hemolysin (Lys) is a flavonoid compound that exerts an anti-tumor effect by regulating Nrf2 signaling to induce ferroptosis in HCT116 and SW480

CRC cells [42].

4. Conclusion

Ferroptosis theory is a new type of cell death discovered recently. This paper summarizes the related mechanisms of ferroptosis and its research progress in gastrointestinal tumors in recent years. A large number of studies have shown that ferroptosis has great potential in tumor therapy. However, the candidate genes identified in different studies are largely inconsistent, and their mechanism of action has not yet reached a consensus, which still needs further study. Of course, while benefiting, we must also deeply realize that everything has two sides. In clinical applications, we must objectively understand the impact of ferroptosis. At present, scholars have gradually expanded the scope of research on ferroptosis. The heterogeneous treatment of ferroptosis in triple-negative breast cancer [43] provides a new idea for immunotherapy of tumors. The therapeutic effect of ferroptosis needs to be further explored. In summary, the discovery of ferroptosis has opened up a new vision for the clinical treatment of tumors, but whether patients can benefit from it still needs further scientific research.

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