International Journal of Biomedical Science and Engineering
2023; 11(4): 54-60
http://www.sciencepublishinggroup.com/j/ijbse
doi: 10.11648/j.ijbse.20231104.12
ISSN: 2376-7227 (Print); ISSN: 2376-7235 (Online)

The Developments and Advancements in Ferroptosis Research for the Treatment of Pancreatic Cancer: A Review

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To cite this article:
Jingchang Zhang, Yongfu Zhao. (2023). The Developments and Advancements in Ferroptosis Research for the Treatment of Pancreatic Cancer: A Review. *International Journal of Biomedical Science and Engineering*, *11*(4), 54-60. https://doi.org/10.11648/j.ijbse.20231104.12

Received: October 10, 2023; **Accepted**: December 5, 2023; **Published**: December 6, 2023

Abstract: Pancreatic cancer (PC) is a highly lethal form of cancer that presents significant challenges for early detection. It rapidly metastasizes and often shows resistance to conventional chemotherapy. Consequently, the prognosis for most patients is bleak. Despite substantial advances in medical research, the number of viable treatment options remains limited, highlighting the urgent need for innovative strategies to improve patient outcomes. Ferroptosis is a unique type of cell death triggered by excessive iron levels. It sets itself apart from other forms of cell death, such as apoptosis and necrosis, characterized by an overabundance of lipid peroxides and reactive oxygen species. Ferroptosis plays a critical role in sustaining the viability of healthy cells and tissues. However, specific cancerous cells are vulnerable to this process. The resistance of pancreatic cancer cells to chemotherapeutic drugs has become the main reason for chemotherapy failure. Inducing ferroptosis in cancer cells is the best way to overcome chemotherapy resistance. Small molecule drugs can cause iron death through glutathione depletion and lipid peroxidation. Ferroptosis inhibitors may become an adjuvant therapy enhancer, acting with ferroptosis inducers on pancreatic tumor cells. As such, the induction of ferroptosis may offer a promising new avenue for cancer treatment. This article examines PC's iron-induced cell death regulatory mechanism and potential therapeutic applications.

Keywords: Ferroptosis, Pancreatic Cancer (PC), Glutathione Peroxidase 4 (GPX4), System XC, Tumor Microenvironment (TME)

1. Introduction

During the 1990s, Tan et al. conducted a study on immortalized mouse neural cells (HT-22) using glutamate to examine the impact of oxidative stress on neuronal cells. The research revealed that glutamate competes with cysteine uptake, which results in decreased glutathione and ultimately leads to cell oxidative death. In 2008, Seiler et al. discovered that lipid peroxidation plays a significant role in cell death in glutathione peroxidase 4 (GPX4) knockout cells. They suggest that GPX4 uses oxidative stress to activate a new cell death pathway [1]. Further research indicates that apoptosis or necrosis cannot explain the cell death pattern that occurs in some instances. In 2012, Dixon and colleagues officially named this pattern of cell death as ferroptosis. Iron is a crucial element that plays a vital role in several essential metabolic processes in the body.

Maintaining an appropriate balance of intracellular iron content is crucial for normal physiological functioning. This balance is primarily regulated by transferrin and ferritin. Excessive accumulation of iron ions can lead to "iron enrichment" and cause cell death, known as ferroptosis. Ferroptosis is a type of cell death that depends on iron and is characterized by the accumulation of intracellular lipid reactive oxygen species (L-ROS). Reactive oxygen species (ROS) are oxygen-free radicals and peroxides produced during oxygen metabolism in living organisms. All of them have oxygen atoms and exhibit oxidizing solid properties. Reactive oxygen species (ROS) can interact with polyunsaturated fatty acids in the lipid membrane, leading to lipid peroxidation and producing lipid reactive oxygen species (L-ROS). When the concentration of L-ROS increases, it can cause cellular oxidative stress and damage [2, 3]. Iron ions can promote the formation of reactive oxygen species (ROS) within cells through the Fenton reaction. In this reaction, iron

acts as a catalyst for the breakdown of hydrogen peroxide (H_2O_2), generating hydroxyl radicals that increase phospholipid oxidation and membrane lipid degradation. It is worth noting that ROS are highly reactive molecules that can cause significant damage to cellular components. Therefore, the role of iron as a mediator of ROS formation has substantial implications for cellular health and is an area of active research in biology and medicine [4]. The formation of L-ROS and oxidative damage to cells are worsened by these factors. Ferroptosis is distinct from other forms of cell death, such as apoptosis, necrosis, and autophagy. Morphologically, ferroptosis cells show specific mitochondrial contraction and increased mitochondrial membrane density without other common features of cell death [5]. Deposition of ion iron results in oxidative cell death via intracellular ROS increase, damages to redox homeostasis, membrane lipid peroxidation, excessive oxidative stress, and reduced antioxidant capacity [6]. In addition, antioxidants and iron chelators can inhibit ferroptosis. Many upstream pathways lead to an imbalance in the production and degradation of L-ROS within cells, ultimately leading to ferroptosis [7].

2. Inhibition of Cysteine Glutamate Transporter System XC-induced Ferroptosis

System XC is a transporter found on the plasma membrane that moves molecules in the opposite direction. It consists of two subunits - a light chain subunit, which is encoded by SLC7A11, and a heavy chain subunit, which is encoded by SLC3A2. The light chain subunit is responsible for transporting specific molecules [8-10]. Cystine is quickly converted to cysteine, which is then used to produce glutathione (GSH). Glutathione is a tripeptide consisting of cysteine, glutamic acid, and glycine. The thiol group structure present in glutathione can be oxidized and dehydrogenated, making it an essential antioxidant and free radical scavenger in the body [11]. GPX is a peroxidase-degrading enzyme, and glutathione is an essential cofactor that activates it [12]. GPX, an enzyme that plays a crucial role in maintaining the balance of oxidation and reduction in cells, helps protect cells from oxidative stress caused by lipid damage and prevents cell death. However, the absorption of cysteine, a precursor for GPX synthesis, can be inhibited by certain ferroptosis inducers that target the system XC. This leads to a decrease in GPX activity, resulting in a reduction of the cell's antioxidant capacity. Consequently, the levels of L-ROS increase, leading to ferroptosis [13]. Inhibiting the system XC, which transports cysteine glutamate, is an essential pathway in inducing ferroptosis.

3. p53 Participates in Ferroptosis

P53, a classic tumor suppressor, regulates cell cycle, aging, and apoptosis [14, 15]. It has been discovered through research on cell death mechanisms that p53 not only triggers cell apoptosis but also plays a critical role in regulating ferroptosis in specific cancer cells [16, 17]. The activation of p53 led to a significant decrease in the expression of SLC7A11 in cells. Conversely, when p53 was upregulated, the mRNA and protein expression of SLC7A11 in cells decreased as well. On the other hand, when the p53 gene was downregulated, it eliminated the inhibition of SLC7A11 in cells [18, 19]. Further research indicates that the antioxidant capacity of cells significantly decreases upon activation of the p53 gene [20]. Zhang et al. concluded that inhibiting the expression of SLC7A11 by activating p53 leads to a decrease in system XC activity, thereby regulating ferroptosis [21]. It could be stated that, aside from inhibiting system XC activity, p53 has been observed to play a role in the mediation of ferroptosis by targeting diamine acetyltransferase and mitochondrial glutaminase, which are involved in the regulation of glutamine metabolism [22, 23].

4. Other Pathways of Ferroptosis

GPX4 is a member of the GPX family and is an essential participant in maintaining the intracellular redox equilibrium. Certain inducers of ferroptosis, such as RSL3 and DP17, function by directly inhibiting GPX4. This, in turn, reduces the cell's antioxidant capacity and eventually leads to ferroptosis. Ferroptosis inhibitor protein 1 (FSP1) is a catalytic oxidoreductase that reduces ubiquitin ketones (coenzyme Q10, CoQ10). Ubiquinone is a lipophilic radical scavenger. FSP1 achieves CoQ10 regeneration through the utilization of NAD (P) H, allowing it to prevent ferroptosis caused by GPX4 deficiency. The FSP1 CoQ10-NAD (P) H pathway, an autonomous, parallel system, works in collaboration with GPX4 to counteract ferroptosis caused by elevated L-ROS levels [24]. Nuclear erythroid-related factor-2 (Nrf-2) is a crucial regulatory factor that plays a vital role in the body's antioxidant response. Kelch-like ECH-associated protein-1 (Keap-1) typically promotes the ubiquitination and proteasome degradation of Nrf2 in normal circumstances. However, Keap1 becomes abnormally activated under oxidative stress, causing a disruption in the interaction between Nrf2 and antioxidant response elements and ultimately regulating ferroptosis [25-27]. Heme oxygenase-1 and transferrin are also essential sources of intracellular iron and participate in the code of ferroptosis [28].

5. Ferroptosis and Tumor Microenvironment

Gene changes during PC development can promote the proliferation, metastasis, and invasion of PC cells and affect the tumor microenvironment (TME) [29]. An important histopathological marker of PC progression is the significant change in TME [57]. The three different types of cells in TME are stromal cells, fibroblasts, and immune cells, and the cell intersection between tumors and stromal cells is crucial for tumor progression [30]. Pancreatic TME comprises abundant

mesenchymal cells, among which pancreatic stellate cells (PSCs) play multiple roles in establishing TME [31]. The histopathological feature of PC is its response to the formation of connective tissue in tumors, and PSCs in the pancreas can be activated by cancer cells to produce fibrosis [32]. TME is also associated with the therapeutic resistance of many chemotherapy drugs, and the abnormal proliferation of stromal cells such as PSCs creates an environment that promotes tumor growth, metastasis, and drug resistance [30, 57]. The activation of PSCs is closely associated with autophagy. Recent research has demonstrated that the inhibition of autophagy in PSCs can effectively reduce extracellular matrix (ECM) production levels, as well as inhibit the metastasis, invasion, and proliferation of PC cells. These findings suggest that autophagy plays a vital role in the progression of PC and that inhibiting autophagy in PSCs may be a promising therapeutic strategy for the treatment of this disease [33]. In 2016, Sousa discovered that the secretion of alanine by PSCs depends on the autophagy of PSCs, and alanine plays a unique role in promoting the tricarboxylic acid (TCA) cycle and lipid biosynthesis [32]. Recent research has further explored the specific relationship between PSCs and PCs. The alanine interaction between PSCs and PCs is achieved using solute carrier family one member 4 (SLC1A4), which affects tumor metabolism and growth [34].

Ferroptosis is a form of regulated cell death that involves the release of damage-associated molecular patterns (DAMPs) from dying cells, which in turn mediate inflammation and immune response in the regulation of the TME [35]. The toll-like receptors in PC participate in the release of DAMPs and activate the proinflammatory pathway, creating a favorable microenvironment for tumor cell proliferation [36]. A recent study suggests that the release of DAMPs mediated by ferroptosis can promote tumor growth by driving the polarization of macrophages in TME [37]. The study by Dai et al. demonstrated that ESCRT-III, as a negative regulatory factor for ferroptosis in tumor cells, significantly affects regulating lipid peroxidation and DAMP release [38]. In another study, a diet rich in glutathione peroxidase 4 (GPX4) or iron significantly increased 8-OHG, which mediates macrophage infiltration through the membrane elongation protein 173 (TMEM173) pathway and activation, the results show that yields can be increased. Resulting in the release of oxidized DAMP. This suggests that cell death-induced DAMP release, as a component of the TME, plays a potential pathological role in the occurrence and progression of cancer [46].

6. The Unique Mechanism of Ferroptosis in PC

As mentioned earlier, GPX4 and SystemXC are key regulatory components in the ferroptosis process. Many substances interfere with ferroptosis by affecting the metabolism of GPX4 or the normal function of the XC subunit of the system. For example, BECN1 can combine with SLC7A11 to form a complex that inhibits SystemXC function [39]. As a chaperone protein, HSPA5 can form a complex with GPX4 and inhibit the degradation of GPX4 [40]. Using fluorescent probes, the researchers found that cysteine was significantly depleted [41].

Numerous investigations have demonstrated the crucial role of an iron-binding nucleoprotein in facilitating the resistance of human PC cells to ferroptosis. This nucleoprotein serves as a redox sensor for ferroptosis and functions as a target gene for NFE2L2/NRF2. Upregulation of NFE2L2 restricts DNA damage, intracellular transport, and extracellular release of HMGB1 by iron-binding nucleoproteins. In the absence of this nucleoprotein, the interaction between BECN1 and HMGB1 activates ACSL4, thereby augmenting autophagy-dependent ferroptosis [42]. STAT3, a positive regulatory factor for ferroptosis in PC cell lines, stimulates ferroptosis by instigating lysosomal cell death mediated by cathepsin [43]. On the glucose metabolism front, PDK4 (pyruvate dehydrogenase kinase isoenzyme 4) impedes glucose-dependent ferroptosis. PDK4 predominantly obstructs ferroptosis by suppressing pyruvate oxidation in PC cells, inhibiting entry into the tricarboxylic acid cycle, and enabling the formation of fatty acids [44]. Recent investigations have confirmed the involvement of glutamic oxaloacetic transaminase 1 (GOT1) in PC cell death induced by iron overload. GOT1 restrains mitochondrial metabolism and redox levels by inhibiting cysteine input, GSH production, and the synergistic effect between GPX4 and GOT1. Consequently, the sensitivity of PC cell lines to ferroptosis is enhanced, thereby triggering ferroptosis [45]. In Kras-driven PC, ferroptosis, induced by a high iron diet or GPX4 consumption, triggers the liberation of oxidized nuclear bases (such as 8-OHG), thereby activating the TMEN173-dependent DNA sensor pathway. This ultimately leads to macrophage infiltration and activation of Kras-driven PC. Consequently, pharmaceutical, and genetic inhibition of macrophage failure or the 8-OHG-TMEM173 pathway curbs the incidence of pancreatic tumors mediated by ferroptosis [46].

7. New Treatment Strategy for PC Targeting Ferroptosis

PC, as a high-mortality cancer, is increasingly becoming a common cause of cancer death. It is expected that by 2030, PC will become the second leading cause of cancer deaths [47]. PC is often asymptomatic until it reaches an advanced stage, making early diagnosis challenging. Consequently, the prognosis for PC is generally poor, with a 5-year survival rate of approximately 10% in the United States. This is since many patients, approximately 80-85%, are unresectable or have distant metastasis at the time of diagnosis [48]. Patients suffering from PC are often categorized into four distinct groups: resectable, borderline resectable, local invasion and metastasis, and distant metastasis. Treatment options for this disease typically involve a combination of surgery, chemotherapy, radiotherapy, and palliative care, each of which is prescribed based on the stage of the disease. Although

surgical intervention is currently the most effective therapeutic option, adjuvant chemotherapy may also be recommended in certain cases. However, it should be noted that surgical resection is only viable for a small subset of patients with non-metastatic resectable tumors [49]. Therefore, surgical resection and adjuvant chemotherapy are standardized treatments for resectable PC patients [50, 51]. For tumors that are borderline resectable or locally advanced and unresectable, chemotherapy can be a potential treatment option. In cases where the cancer has metastasized, commonly used chemotherapy drugs include paclitaxel and gemcitabine. For advanced patients, palliative medicine and supportive care are also available. Unfortunately, despite the use of traditional therapies such as chemotherapy and radiotherapy, the 5-year survival rate has not improved, and the mortality rate of pancreatic cancer continues to increase each year. Given these discouraging clinical results, there is a pressing need for the development of new and effective therapies [52]. Therefore, developing new treatment methods is still an urgent task for the clinical treatment of PC.

Emerging treatment strategies, such as genomics, matrix therapy, and immunotherapy, although not standardized therapies have shown considerable therapeutic potential [53]. Immunotherapy has made significant strides in recent years, exhibiting robust anti-cancer effects through the amalgamation of vital treatments such as immune checkpoint blockade, tumor vaccines, and chemotherapy. The integration of dependable immunopharmacological biomarkers can further enhance the prognosis of the treatment process, leading to improved patient outcomes [54, 55]. The latest research has delved into the immunotherapy approach for PC, which aims to limit the spread of the disease by providing antigen specificity, improving T cell function, and reducing the immunosuppressive impact of TME components. Moreover, novel interstitial targeted therapy could potentially enhance the outlook for patients with PC. However, due to the intricate nature of TME in PC, interstitial targeted therapy still presents significant obstacles [56, 57]. Combining complementary interstitial targeted and immune-targeted treatment modes, utilizing changes in TME components, has demonstrated good therapeutic prospects [58]. Several high-throughput sequencing methods were utilized to categorize PC into mesenchymal and epithelial subtypes, while distinct microbiome patterns were discovered for PC. The goal is to leverage different components of TME to offer customized PC treatment in the future. Earlier research has indicated that chemotherapy resistance in tumor cells is the primary reason for chemotherapy failure. The most effective method to overcome this resistance is to induce ferroptosis in cancer cells. Small molecule drugs can accomplish this by depleting glutathione, inactivating GPX4, and causing lipid peroxidation [59].

In the review by Nie et al. and Zhang et al., they elucidated the role of ferroptosis in reversing drug resistance in chemotherapy, targeted therapy, and immunotherapy applications [60, 61]. The pathways implicated in ferroptosis in PC represent a promising avenue for clinical intervention. The use of ferroptosis inhibitors as an adjuvant therapy presents a potential strategy to improve treatment efficacy when combined with ferroptosis inducers in cancer cells. Such a therapeutic approach has the potential to enhance clinical outcomes in PC patients [62]. Empirical investigations have established that the FBW7-NR4A1-SCD1 signaling pathway can augment the cytotoxic potential of gemcitabine on pancreatic cancer (PC) cells. This is accomplished through the activation of ferroptosis, which serves as a promising target for chemotherapy. By reducing the drug resistance of chemotherapy agents, this pathway provides a novel approach to comprehensive clinical treatment [63]. In addition, PC with ARAS mutation can be treated by targeting BCAT2 or controlling BCAA in diet, which indicates a potential therapeutic approach to overcome sorafenib resistance [64].

New evidence suggests that targeting the MGST1 redox-sensitive pathway may be a promising strategy for treating PC, as MGST1 expression is associated with poor prognosis in PC patients [65]. It is noteworthy that most studies on pancreatic cancer are based on cellular research and animal experiments, with limited reporting on clinical treatment results. At the genetic level, a prognosis model for pancreatic cancer was established by screening ferroptosis-related genes (FRGs) that are associated with the prognosis of pancreatic cancer using patient samples [66, 67]. The prediction model utilizing six genes and FRGs constructed by the TCGA-PAAD cohort demonstrates notable efficacy and consistency in forecasting the prognosis of PC. Such findings furnish a dependable foundation for comprehending the part played by FRGs in PC and identifying potential therapeutic targets.

In summary, there is a need for further research and confirmation in the field of cancer treatment for ferroptosis. It is important to believe that by developing treatment strategies for ferritic cell death, we can overcome the drug resistance of cancer cells. With the advent of nanomedicine, there is a great opportunity to develop more effective and targeted ferroptosis therapies by combining iron-based nanomaterials with other components that cause ferroptosis [68]. Despite the progress that has been made in treating cancer, there remain several challenges that need to be addressed. For instance, it would be valuable to explore how epigenome editing can be used to enhance tumor response to ferroptosis, as well as to understand the relative efficacy of ferroptosis induction compared to immunotherapy. Furthermore, it is worth investigating the therapeutic potential of lipophilic free radicals in managing lipid ROS, lipid peroxidation, and ferroptosis-induced damage, as well as the flexibility of lipid metabolism in cancer cells in maintaining sensitivity to ferroptosis. Overall, a deeper understanding of the regulatory mechanism and metabolic pathway of ferroptosis in PC could prove to be invaluable in the quest for better cancer treatments.

8. Conclusion

PC is a type of cancer that unfortunately has a high mortality rate and is known to metastasize early and be

diagnosed late, making effective treatment challenging. Moreover, the development of drug resistance further complicates treatment options. However, research has revealed that ferroptosis, a type of cell death caused by intracellular iron buildup and lipid peroxidation, plays a vital role in regulating the progression of many diseases, including PC. This article explains the regulatory mechanism and signaling pathway of ferroptosis in developing PC from a metabolic perspective. The regulation of ferroptosis is mainly influenced by various regulatory substances that affect lipid peroxidation, iron phagocytosis, or iron accumulation, particularly in terms of iron and lipid metabolism. The regulation of ferroptosis through SystemXC and GPX4 primarily involves controlling the expression of GPX4, regulating the core components of SystemXC, or influencing amino acid metabolism. It is worth noting that research has suggested that combining ferroptosis inhibitors with chemotherapy drugs may enhance cancer cell resistance. Therefore, this article aims to explain the mechanism of ferroptosis in PC, which can help develop inhibitors or inducers for ferroptosis. Ultimately, targeted ferroptosis therapy can become a promising treatment option to improve the survival rate of patients.

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Conflicts of Interest

The authors declare no conflicts of interest.

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