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Metal-related cell death and its application in pancreatic cancer

Short title: Cell death in pancreatic cancer

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Abstract

As a highly aggressive tumor of the digestive tract, pancreatic cancer has a high mortality rate and poor treatment outcomes. The five-year survival rate for patients is distressingly low, and the recurrence chance remains unacceptably high even with successful treatment. Surgical procedures and chemotherapy are main treatments of pancreatic cancer besides the surgical procedures are the only effective treatment at present. But the cancer cells can easily develop resistance to chemotherapy agents, which lead to low treatment efficacy and high mortality in pancreatic cancer. Additionally, early diagnosis of pancreatic cancer is challenging due to the absence of obvious symptoms, making surgical intervention unattainable in early stage. However, the pancreatic cancer cells show unique changes at genetic and cellular levels which make pancreatic cancer cells sensitive to metal-related cell death or have some characteristics related to metal-related cell death. These changes and characteristic could be utilized for treatment and diagnosis in pancreatic cancer. Therefore, our motivation is to explain the potential of metal-related cell death in treating this aggressive cancer. This review begins by analyzing types of metal-related cell death: ferroptosis,

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cuproptosis, and lysozincrosis. Each form is evaluated based on its unique features and related metabolic pathways. By examining the key characteristics of metal-related cell death modalities, their primary metabolic patterns, and their interactions with pancreatic cancer, our goal is to point the direction to identify potential therapies and treatments. Our review expands the possibilities for utilizing metal-related cell death and instills hope for its future potential in pancreatic cancer treatment.

Keywords: Metal-Related Death; Pancreatic Cancer; Ferroptosis; Cuproptosis; Lysozincrosis

HIGHLIGHTS

1. The regulatory mechanisms associated with ferroptosis in cancer.
2. Mechanisms involved in the regulation of cuproptosis in cancer.
3. Mechanisms associated with lysozincrosis in cancer.
4. Unique mechanisms of ferroptosis in pancreatic cancer.
5. Ferroptosis and the treatment of pancreatic cancer.
6. Prospect of cuproptosis in treatment of pancreatic cancer.

1 Introdution

Pancreatic cancer is an aggressive tumor in the digestive tract. The 90% pancreatic cancer cases arises from the duct epithelium, specifically pancreatic duct adenocarcinoma[1]. In the early stages of the cancer, patients usually do not have noticeable symptoms, which poses challenges for early diagnosis. Pancreatic cancer cells have an strong tendency to invade surrounding tissues, which obstruct early diagnosis[2]. Currently, the dominant

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treatment strategy involves prioritizing surgical intervention combined with adjuvant chemotherapy. However, these cancer cells easily develop resistance to chemotherapy drugs, which hinders treatment effectiveness. The emergence of drug resistance in pancreatic cancer cells is strongly associated with the manifestation of undetected metastases[3]. Gemcitabine, the first-line chemotherapy medication, shows some effectiveness in pancreatic cancer treatment. However, the development of gemcitabine resistance significantly reduces its efficacy, which is attributed to a combination of factors including pancreatic cancer cells, cancer stem cells, and the tumor microenvironment[3]. Although surgery is the only curative option for pancreatic cancer, the five-year survival rate is only 20%[4]. Moreover, patients face a high risk of recurrence, ranging from 70% to 80% after treatment. The low five-year survival rate and the risk of recurrence mean that macroscopic surgical resection is often unable make to effectively prolong survival in these patients, and often results in recurrence. Unfortunately, pancreatic cancer is often diagnosed at advanced stages, making surgical intervention hard to exert. This, along with other factors, makes pancreatic cancer a complex disease with a high mortality. This has led researchers to consider the potential of exploring and identifying strategies to inhibit pancreatic cancer progression at the microscopic level.

In recent years, researches on metal-related cell death and tumour-associated metal ions has generated progress, prompting a shift in focus towards practical applications. Novel forms of programmed cell death, like ferroptosis, lysozincrosis, and cuproptosis, are distinct from traditional mechanisms, as apoptosis, autophagy, and pyroptosis. Ferroptosis, first identified in 2012[5], occurs due to excessive levels of iron leading to intracellular lipid peroxidation and consequent cell death[6]. Lysozincrosis is triggered by high concentrations of zinc that

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hinder adenosine triphosphate (ATP) synthesis, resulting in non-apoptotic cell death. Cuproptosis arises when copper ions directly bind to acylated components in the tricarboxylic acid cycle pathway, leading to aberrant accumulation of acylated proteins and the depletion of iron-sulfur cluster proteins. Consequently, this mechanism triggers toxic protein stress reactions and cell death. These specific metal-related cell death have prompted the question of whether it is possible to induce pancreatic cancer cell death, thereby accelerating the death of pancreatic cancer cells and prolonging the survival cycle of pancreatic cancer patients, or even curing pancreatic cancer. Under such premises with a gradual deepening research on pancreatic cancer, unique changes of pancreatic cancer cells have been found. For example, pancreatic cancer cells may be sensitive to ferroptosis due to special gene mutations. Pancreatic cancer cells demonstrate unique changes that link pancreatic cancer to a process termed cell death through metal ion involvement, helping further research on treatment and diagnosis of pancreatic cancer.

Research on metal-related cell death has generated extensive knowledge, arousing interest in various fields, in which ferroptosis exhibits significant potential for short-term applications. Metal-related cell death provides a novel direction to tackle the obstructions of pancreatic cancer treatment[7].

2 Ferroptosis

2.1 Overview and Basic Characteristics of Ferroptosis

The fundamental basis of ferroptosis is primarily the result of unstable hydroxyl radicals produced through iron-catalyzed Fenton reactions[8]. This procedure promotes the oxidation of polyunsaturated fatty acids and ultimately leads to the formation of lipid peroxides[9]. The

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accumulation of lipid peroxides damages cellular membranes, increasing their susceptibility and ultimately leading to cell death[10]. Consequently, the high abundance of iron is a crucial factor driving the occurrence of ferroptosis, with lipid peroxidation acting as the direct trigger that makes ferroptosis exhibits diverse characteristics in biochemical and morphologic aspects .

In terms of its biochemical attributes, ferroptosis cells inevitably exhibit elevated iron accumulation owing to the dependence of the ferroptosis mechanism on iron ions. Ferroptosis is initiated by iron-driven lipid peroxidation the disturbance of iron ions causing lipid peroxidation, leading to an excess of lipid peroxides in ferroptosis cells[11].

Morphologically, ferroptotsis cells display impairments of various organelles, primarily triggered by membrane disruptions[12]. Remarkably, ferroptosis elicits unique transformations in mitochondria, as demonstrated by their decreased size, lowered cristae density, increased mitochondrial membrane density, and heightened frequency of mitochondrial membrane rupture[11,12].

As a regulated form of cell death distinct from apoptosis, ferroptosis involves a complex interplay of crucial molecules in its procedure[6]. The primary contributors to the ferroptosis process include SLC7A11, which acts as the principal conduit for transporting glutathione precursors, GPX4 and GSR, are enzymes responsible for glutathione oxidation and reduction. TFR1, the main protein responsible for transporting iron, plays a vital role in coordinating the complex process of ferroptosis in cells. These specialized molecules play crucial roles in determining cell death during ferroptosis.

The observable characteristics of ferroptosis cells provide insight into methods of

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inducing or inhibiting cell ferroptosis. By regulating the levels of iron, glutamic acid, and cystine, it is possible to influence the course of ferroptosis processes. Targeted pharmacological interventions can regulate specialized molecules involved in ferroptosis and provide an avenue for precise control over this complex cellular phenomenon. The features of ferroptosis cells offer insights for developing novel manipulation approaches.

2.2 Metabolic Pathways of Ferroptosis

The onset of ferroptosis is tightly linked with the metabolic pathways regulating its associated components. The excessive iron is crucial to the development of ferroptosis, leading to lipid peroxidation[13]. As a result, the occurrence of ferroptosis largely relies on the complex interplay of iron metabolism, lipid metabolism, and glutathione peroxidase metabolism. These metabolic processes collectively determine the outcome of ferroptosis events, revealing the mechanisms that drive this cellular phenomenon(**Figure 1**).

2.2.1 Iron Metabolism

Iron plays a critical role in the body's metabolic processes, including oxygen transportation, DNA biosynthesis, and serving as a coenzyme in the tricarboxylic acid cycle and electron transfer chain, influencing ATP synthesis. The body maintains a precise physiological threshold for iron levels to strike a delicate balance between its essential function and optimal quantity. Thus, iron’s multifaceted functions contribute to vital physiological processes.

Typically, iron binds to transferrin and enters cells via the cytosolic pathway facilitated by the transferrin receptor TfR1 on the cell membrane. This serves as the primary route for iron acquisition in almost all cell types and the uptake of iron mediated by transferrin and its

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receptor plays a crucial role in the endocytosis of transferrin-bound iron, making it a prerequisite for ferroptosis occurrence. This is one of the primary sources of iron required for initiating ferroptosis. Afterwards, it enters iron-demanding areas, where it enters the cell nucleus via TfR1 mediation. Within the nucleus, it transforms to Fe^{2+} and then transported to the labile iron pool in the cytoplasm with the assistance of divalent metal transporter 1[14,15]. The ferritin light chain and ferritin heavy chain 1 sequester the remaining iron[9,16]. It is important to mention that lysosomal degradation of these ferritins can lead to an increase in intracellular free iron[17]. When there is a failure to store or export intracellular free iron, it accumulates in the cytoplasm, catalyzes the Fenton reaction, and leads to several lipid peroxidation events inside the cell. Eventually, this results in producing toxic reactive oxygen species (ROS)[16,18], which damages multiple cellular membrane structures and consequently induce cell ferroptosis[19]. This pathway highlights the correlation between ferroptosis and a cell's ability to uptake and store iron. Specifically, when a cell takes in more iron than it can use and surpasses its iron storage capacity, the excess iron remaining in the cell can trigger lipid peroxidation, leading to ferroptosis[16].

2.2.2 Lipid Metabolism

Biological cells contain phospholipids composed of hydrophilic phosphate groups and hydrophobic fatty chains, resulting in both hydrophilic and lipophilic domains within a phospholipid molecule[8]. This unique property allows them to form a bilayer structure known as a biofilm. Disruption of the biofilm structure occurs when the phospholipid molecules undergo oxidation, resulting in functional impairment. This disruption is a significant factor in initiating cell ferroptosis.

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Phospholipids and other lipids with unsaturated double bonds can self-oxidize in the presence of oxygen. This process results in a free radical chain reaction[16]. The presence of divalent iron or comparable metal cations increases the formation of extremely reactive hydroxyl radicals through peroxides. Hydroxyl radicals remove hydrogen from unsaturated phospholipids or lipids, leading to the creation of lipid free radicals that initiate a chain reaction of free radicals[18]. Lipid free radicals react with oxygen to form lipid peroxidation free radicals then react with other unsaturated lipids and produce additional lipid free radicals. This free radical chain reaction continues until termination[16].

Essentially, this process comprises a free radical chain reaction of polyunsaturated fatty acids (PUFAs) triggered by iron ions or similar metal cations, resulting in the generation of toxic phosphate hydroperoxides (PLOOH). These hydroperoxides not only harm the structure of the cell membrane but also have detrimental effects on cells[8]. This mechanism is fundamental in the occurrence of ferroptosis.

The specialized lipid peroxides, namely phospholipids PE-AA and PE-AdA derived from arachidonic acid (AA) or adrenic acid (AdA), are the primary facilitators in ferroptosis. These specific lipid molecules undergo either enzymatic-mediated reactions or self-oxidation, producing lipid peroxides. In the presence of divalent iron ions, these peroxides eventually become lipid peroxidation radicals. The lipid peroxidation radicals resulting from this process further oxidize phospholipids found within cell membranes and subcellular organelle membranes, disrupting essential membrane fluidity and properties. Ultimately, these changes lead to ferroptosis at a cellular level.

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2.2.3 Glutathione Peroxidase Metabolism

Glutathione plays a vital role as an intracellular antioxidant and a key regulator of ferroptosis. Specifically, glutathione (GSH) and glutathione peroxidase 4 (GPX4) impede the function of lipid oxidase (LOX)[19]. This impediment helps remove lipid peroxides produced due to iron accumulation, effectively countering lipid bilayer peroxidation and preventing cell membrane damage[20].

The production of glutathione within cells mainly relies on System Xc-, which functions as a membrane sodium-dependent reverse transporter for cysteine and glutamic acid[14]. This system is composed of a disulfide heterodimer consisting of the light chain subunit SLC7A11 and the heavy chain subunit SLC3A2, where SLC7A11 acts as the primary transporter. The p53 gene governs the regulation of SLC7A11[16].

The Xc- system has a dual function of transporting intracellular glutamic acid and extracellular cystine into the cell. Subsequently, thioredoxin reductase 1 catalyzes the conversion of extracellular cystine into cysteine. Finally, cysteine conjugates with glutamic acid and glycine, resulting in the production of GSH[18].

Under the action of GPx4, GSH is oxidized to form GSSG. This oxidation process reduces toxic phosphate hydroperoxides derived from polyunsaturated fatty acids to harmless phospholipids. This procedure effectively decreases the production of harmful lipid reactive oxygen species (ROS) and effectively prevent ferroptosis[6,18,21].

To maintain sufficient levels of GSH, glutathione reductase (GSR) must assist in reducing oxidized GSSG back to GSH. This reduction process requires NADPH participation[15].

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NADPH plays a crucial role in providing hydrogen for the reduction of GSSG to GSH. The presence of VDACs, proteins located on the outer membrane of mitochondria, is necessary for the availability of this hydrogen. VDACs are responsible for maintaining the permeability of the outer membrane and are distributed throughout mitochondria. Presently, three subtypes of VDACs have been identified: VDAC1, VDAC2, and VDAC3. When the voltage-dependent anion-selective channel (VDAC)2/3 is blocked, it causes a decrease in levels of nicotinamide adenine dinucleotide phosphate($NADP^+$), which leads to a reduction in reduced nicotinamide adenine dinucleotide phosphate (NADPH) levels. NADPH is critical for providing the necessary hydrogen to convert GSSG to GSH. The decrease in NADPH results in a decrease in intracellular GSH, triggering the accumulation of intracellular lipid ROS and the onset of ferroptosis[20]. This same mechanism is also evident in erastin, the ferroptosis agonist, which shows potential for inducing cell ferroptosis.

Conversely, there is a coordinated increase in lipid ROS levels under conditions of cysteine deprivation and glutathione depletion. Cysteine deficiency reduces the cellular uptake and triggers the efflux of GSH, leading to its catabolism outside the cell to maintain intracellular cysteine levels. Thus, inhibiting System Xc- may effectively trigger cell ferroptosis[20].

2.2.4 FSP1 Related Changes

Recent studies have shown that FSP1, also referred to as AIFM2, can prevent cell ferroptosis by inhibiting lipid peroxidation, even without reliance on GPX4 for its activity. This is achieved by regulating CoQ10 levels, which mitigates the accumulation of peroxidized lipid free radicals in cells[22]. It is important to note that the GPX4 pathway

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operates alongside this pathway, and they collaborate to effectively combat cell ferroptosis[23].

In summary, ferroptosis is a culmination of various processes, triggered by excessive iron in the cell, resulting in the production of unstable hydroxyl radicals through the Fenton reaction. The production of excessive hydroxyl radicals through the Fenton reaction results in oxidative stress and cell death. The cell comprises unsaturated phospholipids and other lipids that contribute to diverse membrane structures. These structures uphold the cell's normal physiological functions. The unsaturated phospholipids and lipid molecules react, causing the generation of lipid radicals and a chain of free radical reactions. This oxidation process continuously damages different lipid membrane structures in the cell, including the inner membrane structure. Besides, the oxidation of glutathione is catalyzed by glutathione peroxidase using System Xc- and cystine-generated glutathione. This process reduces harmful phosphate hydroperoxides (PLOOH) which form when polyunsaturated fatty acids (PUFAs) undergo oxidation. As a result, it prevents cell ferroptosis[19]. To maintain GSH levels, GPX4 oxidizes GSH into GSSG, which is regenerated by glutathione reductase (GSR) using NADPH. VDACs provide NADPH to support this process, enabling cells to withstand ferroptosis. Overall, ferroptosis occurs as a consequence of these various processes, and alterations to these processes may initiate or hinder ferroptosis in cells, with potential implications for future applications of ferroptosis .

2.3 Ferroptosis and Pancreatic Cancer

Pancreatic cancer, a highly aggressive malignancy of the digestive system, have surgical resection as its only curative option. However, nonspecific early symptoms lead to 90% of

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cases being diagnosed at advanced stages, precluding surgery[7]. While chemotherapy remains the mainstay treatment, rapid development of drug resistance often renders it ineffective. Recent studies suggest ferroptosis modulation may selectively target pancreatic cancer cells, offering a novel therapeutic approach[19]. Future directions induce using ferroptosis inducers as targeted and exploring ferroptosis-related biomarkers for early detection.

2.3.1 Intracellular Changes Associated with Ferroptosis in Pancreatic Cancer

2.3.1.1 KRAS Gene Mutation Related

Research findings indicate that KRAS gene mutations are present in 90% of patients diagnosed with pancreatic cancer[24]. These mutations stimulate the proliferation of tumor cells and disrupt cellular metabolism. Specifically, KRAS mutations decrease the expression of pro-apoptotic proteins and increase the expression of anti-apoptotic proteins, ultimately inhibiting apoptosis and potentially leading to the resistance of pancreatic cancer cells to conventional chemotherapy drugs. KRAS mutations increase iron intake and decrease iron storage capacity in tumor cells, disrupting iron homeostasis. This results in elevated levels of reactive oxygen species (ROS) in KRAS mutant tumor cells compared to normal cells. Consequently, KRAS mutant pancreatic cancer cells exhibit increased sensitivity to ferroptosis.

To counteract the harmful effects of excessive ROS, these tumor cells with KRAS mutations produce large amounts of glutathione (GSH). In KRAS-mutated tumor cells, the active expression of System Xc-, which is responsible for importing cystine necessary for GSH synthesis, is significantly increased compared to normal cells[25,26]. Therefore,

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targeting System Xc- in pancreatic cancer cells and promoting ferroptosis could potentially serve as a valuable therapeutic strategy in the future management of pancreatic cancer.

Although the KRAS mutation increases the sensitivity to ferroptosis, it also promotes the proliferation, metastasis, and invasion of pancreatic cancer cells, affecting both the tumor microenvironment (TME) and metabolic reprogramming[27]. Ferroptosis, a regulated programmed cell death (PCD) involves the release of damage-related molecular patterns (DAMPs), plays a critical role in this process. Damage-associated molecular patterns (DAMPs) act as mediators in regulating inflammation and immune response in the tumor microenvironment(TME). Studies suggest that DAMPs released by tumor cells killed through ferroptosis can induce macrophage polarization in the TME of pancreatic ductal adenocarcinoma(PDAC) cells. This polarization results in the transformation of macrophages into the M2 type, further promoting tumor growth[27]. These findings suggest that ferroptosis could be a double-edged sword in pancreatic cancer, may exacerbating the cancer development.

2.3.1.2 Cytoplasmic Aspartate Aminotransferase Related

NADPH is a vital role in cellular redox reactions and biosynthesis. In pancreatic cancer cells, the production of NADPH depends on the malate aspartate shuttle. This process is mainly regulated by the KRAS mutation, which controls cytosolic aspartate aminotransferase (GOT1) activity[28]. It is crucial to note that in pancreatic cancer cells, NADPH production heavily relies on this process. While inhibiting GOT1 in normal cells does not have significant consequences, as NADPH production does not heavily rely on these pathways, the dependency of pancreatic cancer cells on GOT1 provides a potential avenue for inducing

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ferroptosis in cancer cells. Previous experiments have also shown that on the premise of inhibiting GOT1, the use of ferroptosis inducers such as erastin or inhibiting the input of glutathione in pancreatic cancer cells can lead to the increase of lipid peroxide in pancreatic cancer cells and finally induce ferroptosis[28]. Therefore, targeting inhibition GOT1 holds potentials for triggering ferroptosis in pancreatic cancer cells.

In pancreatic cancer cells, the production of α-ketoglutarate and aspartate relies on mitochondrial aspartate aminotransferase (GOT2), a key role in this process. The aspartate generated is transported to the cytoplasm and converted by cytosolic aspartate aminotransferase (GOT1), resulting in oxaloacetic acid(OAA). Cytoplasmic malate dehydrogenase 1 (MDH1) converts OAA into malate. Malate is oxidized by malate dehydrogenase 1 (ME1) to produce NADPH[25].

As previously discussed, NADPH plays a crucial role in the ferroptosis process by providing hydrogen for the reduction of oxidized glutathione (GSSG) to its reduced form, glutathione (GSH). However, in pancreatic cancer cells, the reliance on cytosolic aspartate aminotransferase (GOT1) suggests that inhibiting GOT1 decreases NADPH levels. This decrease in intracellular reductant results in accumulated toxic reactive oxygen species (ROS), ultimately triggering the onset of ferroptosis.

2.3.2 Ferroptosis and Treatment of Pancreatic Cancer

2.3.2.1 Diagnosis of Pancreatic Cancer

The low survival rate of pancreatic cancer patients is largely due to the fact that pancreatic cancer is usually diagnosed in advanced stage. However, the above-mentioned discovery of unique changes related to ferroptosis in pancreatic cancer cells provides new

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perspective for early diagnosis of pancreatic cancer. The distinctive changes detected in pancreatic cancer cells offer a chance to improve early diagnosis accuracy by identifying particular biomarkers[29]. Many unique changes mentioned above have shown the specific connection between pancreatic cancer and ferroptosis by providing potential new biomarkers to help early diagnosis of pancreatic cancer, such as iron content, GPX4 expression and ferroptosis sensitivity etc. Some researchers have demonstrated that KRAS mutation can promote pancreatic cancer progression by implanting cells with KRAS mutation into mice and conducting cell experiments[27], with a close relationship to ferroptosis. In short, an assessment of tissue cell iron content, GPX4 expression, and ferroptosis sensitivity that are recognized to be impacted by KRAS gene mutations can enable an more accurate diagnosis of pancreatic cancer in early-stage. If these biomarkers can improve the diagnostic accuracy of early pancreatic cancer, it will be a great breakthrough in pancreatic cancer treatment. This enhanced diagnostic capability potentially extend patients survival timescale to have adequate treatment and provides additional treatment alternatives.

2.3.2.2 Treatment of Pancreatic Cancer

Pancreatic cancer cells have higher levels of intracellular iron compared to normal cells in order to fulfill the demands of rapid cell proliferation, making them more vulnerable to ferroptosis while not damaging normal cells. Therefore, artificailly controlled ferroptosis in pancreatic cancer may become a standalone treatment in the future.

Besides, to counteract the sensitivity to ferroptosis, pancreatic cancer cells exhibit increased activity of System Xc-, enabling the providing sufficient glutathione to mitigate lipid peroxidation[26]. Therefore, strategies such as increasing iron or inhibiting System Xc-

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and reducing glutathione levels can potentially induce ferroptosis as a therapeutic approach in pancreatic cancer[29]. These findings present prospect of deliberately inducing ferroptosis as a targeted therapeutic strategy for pancreatic cancer.

In the context of induced ferroptosis, the integration of this process with radiotherapy has emerged as a promising approach to enhance radiotherapy effectiveness while minimizing associated side effects. By acting as a sensitizer for radiotherapy, this combination approach can effectively decrease the adverse impact of excessive radiation exposure. This, in turn, reduces harm to normal tissues and cells while simultaneously bolstering radiotherapy efficacy[30]. Moreover, the combination of ferroptosis and chemotherapy shows the potential to enhance the cytotoxic effects of anticancer drugs on pancreatic cancer cells. It can also increase their sensitivity to chemotherapy agents, improving the overall effectiveness of chemotherapy [30]. It is worth noting that using a ferroptosis inducer in combination with the anticancer drug gemcitabine shows great prospect in reducing resistance of pancreatic cancer cells to gemcitabine treatment.

Given the aforementioned connections between pancreatic cancer cells and ferroptosis, specifically the increased susceptibility to ferroptosis in pancreatic cancer, inducing ferroptosis is a promising approach in future treatment of pancreatic cancer. Inducing ferroptosis in pancreatic cancer cells has significant potential for clinical applications alongside conventional chemotherapy or radiotherapy, or as a standalone treatment. This emerging approach presents promising opportunities to effectively treat pancreatic cancer and deserves further exploration.

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2.3.2.3Prognosis of Pancreatic Cancer

Numerous studies have demonstrated that the expression of SIRT6 decreases substantially in pancreatic cancer cells compared to normal cells. The low overall survival rate for pancreatic cancer patients and bleak prognosis is largely due to low SIRT6 levels. Furthermore, SIRT6 has a crucial function in regulating ferroptosis and glycolysis by inhibiting the NF-κB signaling pathway. In cancer cells, glycolysis is a significant energy acquisition pathway. NF-κB serves to inhibit cell ferroptosis and promote glycolysis. In contrast, SIRT6 inhibits NF-κB activity. Therefore, higher expression of SIRT6 can promote ferroptosis and restrict cell glycolysis, leading to anticancer effects[31]. Existing cell experiments have demonstrated that the low expression of SIRT6 in pancreatic cancer cells and the up-regulation of SIRT6 expression can increase the ROS content in cells and promote the occurrence of ferroptosis in pancreatic cancer cells[31]. The decrease in SIRT6 expression in pancreatic cancer cells could impede ferroptosis and enhance glycolysis, thus promoting aggressive cancer cell growth. This results in a poor prognosis closely linked to reduced SIRT6 expression[31]. Thus, increasing the expression of SIRT6 shows potentials as a feasible approach to enhance ferroptosis in pancreatic cancer cells, leading to improved prognosis for those affected by this disease.

3 Cuproptosis

3.1 Overview and Basic Characteristics of Cuproptosis

The term “cuproptosis” was first introduced by Peter Tsvetkov in 2022[32]. Further research has demonstrated the harmful consequences of an excessive accumulation of copper, which can cause mitochondrial protein aggregation and cell death. The cuproptisis, which is

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copper-dependent, is in relation to mitochondrial respiration regulation[33]. Cuproptosis is also related to the interaction between copper ions and fatty acylated constituents within the tricarboxylic acid (TCA) cycle.

Cuprotopsis is triggered by copper-dependent fatty acylated protein accumulation along with the reduction of Fe-S cluster proteins, resulting in a distinct cell death process[34]. Therefore, the accumulation of copper and resulting rise in fatty acylated proteins have significant impacts on regulating cuproptosis[35].

In summary, cuproptosis cells characterize the higher intracellular concentrations of copper ions and fatty acylated proteins, along with the reduction of Fe-S cluster proteins. Furthermore, in terms of cytology, cuproptosis induces mitochondrial damage which may lead to cellular respiratory dysfunction.

3.2 Metabolic Pathways of Cuproptosis

In normal cells, three copper transport proteins (SLC31A1 (CTR1), ATP7A, and ATP7B) are primarily responsible for maintaining stable copper levels. SLC31A1 is responsible for copper uptake, while ATP7A and ATP7B aid in copper translocation. The absorption, export, and storage of copper can trigger changes in copper distribution, leading to an increase in the concentration of free copper ions in cells. Several circumstances can result in this phenomenon and lead to cuproptosis. (1) Direct introduction of copper into cells through the use of copper ion carriers such as ES and DSF; (2) increased expression of SLC31A1, indicating the specificity of copper permeation in reducing copper ions; (3) inhibition of glutathione (GSH) synthesis by BSO, which does not release free copper ions; (4) reduction in copper export due to lower ATP7B levels(**Figure 2**).

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Copper ion carriers cause intracellular copper ion levels to exceed the threshold. The excess copper leads to the aggregation of thioacylated proteins and destabilizes Fe-S cluster proteins, resulting in increased cellular protein toxicity stress and ultimately leading to cell death. The critical gene that causes cuproptosis is Ferredoxin1 (FDX1), which is associated with mitochondrial enzyme modification. Mitochondria are the primary target of cuproptosis. FDX1 facilitates the acylation of dihydrothiotransferase (DLAT) and reduces Fe-S cluster proteins by converting Cu^{2+} to Cu^{+}, which ultimately leads to cell death. Excessive binding of Cu (I) to lipid DLAT leads to DLAT oligomerization, which further destabilizes Fe-S clusters and causes cuproptosis. Copper also induces a decrease in Npl4-p97 stability(**Figure 3**).

To prevent the excessive accumulation of copper ions within cells, certain stabilizing mechanisms exist[32]. The intracellular level of Cu is maintained at a steady state by a complex network of Cu-dependent proteins, including copper enzymes, Cu chaperones, and membrane transporters. These proteins work together to regulate the intake, efflux, and utilization of Cu within cells, thereby ensuring intracellular Cu levels remain within a specific range. This regulatory function mitigates the consequences of Cu overload or deficiency. Cu^{2+} binds to growth factor receptors located on the cell membrane in the extracellular space and plays a regulatory role but the process of exerting its function is not fully understood[36].

Copper homeostasis is crucially regulated by copper transporters, and imbalances in this delicate principle can result in cuproptosis[37]. Disturbances in copper homeostasis, such as excessive accumulation or aberrant transportation of copper, may exceed the intracellular copper concentration threshold and cause cellular damage[33]. The accumulation of copper strongly correlates with the onset of cuproptosis.

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3.3 Cuproptosis and Pancreatic Cancer

Emerging evidence suggests that cuproptosis plays a crucial role in the onset and progression of various cardiovascular conditions such as myocardial ischemia/reperfusion (I/R) injury, heart failure, and chronic fatigue[37]. Copper, an indispensable nutrient, exhibits both beneficial and detrimental effects in cellular contexts due to its redox characteristics. Recent developments in the field of transition metal signaling have encouraged interdisciplinary collaboration among researchers, facilitating the translation of basic research in copper chemistry and biology into clinical applications for treatment and diagnosis. This methodology aims to exploit the vulnerabilities associated with copper-dependent diseases. In cancer, the demand for copper as a metal-related nutrient increases with tumor growth and metastasis, challenging the traditional view of copper as solely an active site metabolic cofactor. The copper concentration found in tumor tissue and serum derived from patients with various cancer types, such as breast, lung, gastrointestinal, oral, gallbladder, and pancreatic cancer, has been observed to increase[38]. This heightened accumulation of copper may promote tumor growth by promoting the migration and proliferation of cancer cells. Recently discovered evidence highlights copper a dynamic signal transduction metal and metal allosteric regulator. For example, copper-dependent phosphodiesterase 3B (PDE3B) participates in the process of lipolysis, while mitogen-activated protein kinases 1 (MEK1) and MEK2 are involved in cell growth and proliferation. Additionally, kinases ULK1 and ULK2 play a role in autophagy. Studies showed that cuproptosis programmed-cell-death-related lncRNAs (CRLs) have been linked to PAAD, such as AC005332.6, LINC02041, LINC00857, and AL117382.1[39], and cuproptosis-related genes can provide an essential basis for

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assessing the prognosis of pancreatic cancer patients[40]. These findings reveal the diversified participation of copper, beyond its known metabolic functions.

Although it is found that cancer cells have an increased demand for copper, which means that higher copper content may not only fail to induce cuproptosis to reach the treatment but also may promote cancer cells proliferation and normal tissues damage. But cuproptosis provides a direction to induce a similar apoptotic process by adjusting intracellular fatty acylation proteins and Fe-S cluster proteins, which could be promising approach treatment in pancreatic cancer. But it still needs further research to find out more significant connection between pancreatic cancer and cuproptosis to realize the application of cuproptosis in pancreatic cancer treatment.

4 Lysozincrosis

4.1 Overview and Basic Characteristics of Lysozincrosis

Zinc plays a crucial role in cellular processes. When the concentration of zinc in cells is exceeds moderate levels, it can lead to Lysozincrosis. Lysozincrosis results from the excessive zinc accumulation, which impedes the synthesis of adenosine triphosphate and ultimately leads to non-apoptotic cell death.

Therefore, the increase in zinc concentration is a necessary prerequisite for lysozincrosis, and the damage to mitochondria and lysosomes is the result of excessive zinc concentration, accompanied by a decrease in intracellular ATP. This is a summary of the characteristics of lysozincrosis based on existing research, but further in-depth research on lysozincrosis is still needed.

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4.2 Metabolic Pathways of Lysozincrosis

The mammalian zinc transporters are categorized into two families, the SLC39A and the SLC30A families[41,42]. The SLC39A family comprises 14 members including ZIP1 and ZIP14. These members are responsible for facilitating the transport of zinc ions from the extracellular environment or organelles into the cytoplasm, leading to the absorption and uptake of zinc ions[43]. Conversely, the function of SLC30A family which contains 10 members is opposite to the SLC39A family. Zinc transporter families facilitate the release of zinc ions from the cytoplasm into organelles or the extracellular space, promoting their efflux[43]. Recent researches indicate that these transporter families not only mediate intracellular zinc ion homeostasis but also have complex effects on tumors development and metabolic disorders. Therefore, these transporter families have become key areas of researches in the fields of zinc nutrition and metabolic disorders[44].

The two main groups of zinc transporters show different patterns of distribution within various subcellular organelles, cells, and organs. For example, ZIP4/SLC39A4, ZIP5/SLC39A5, ZIP6/SLC39A6, ZIP10, ZIP14, and ZnT1/SLC30A1 are predominantly located on the cell membrane, while many other zinc transporters are mainly found on different organelle membranes. Regarding tissue and organ distribution, the expression of ZIP4/SLC39A4 and ZnT5 is prominent in small intestinal epithelial cells, whereas ZIP10 and ZnT1 are prevalent in renal epithelial cells. Furthermore, pancreatic gland cells contain ZIP5, ZnT1, and ZnT2, and ZIP8 and ZIP10 are distributed in blood cells, among other locations[44].

Mucous phospholipid TRP channel 1 is a cation channel that allows both Ca^{2+} and

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Zn^{2+}/Fe^{2+} ions to pass through. It is mainly located on the membrane of late endosomes and lysosomes in different types of mammalian cells. The viscophospholipid TRP channel 1 plays a crucial role in lysosomal functionality by releasing both Ca^{2+} and Zn^{2+}. This process is dependent on the levels of lysosomal Zn^{2+}[45](**Figure 4**).

When the intracellular concentration of zinc is abnormal increasing, excessive zinc can cause damage to lysosomes and mitochondria, affecting cellular ATP synthesis and supply, resulting in insufficient intracellular energy and ultimately leading to cell death.

4.3 Lysozincrosis and Pancreatic Cancer

Zinc homeostasis in human cells is tightly regulated by the SLC39A, SLC30A and metallothionein families. Cancer cells may be affected by disruptions in zinc homeostasis or disrupt it themselves. Although decreased serum zinc levels have been observed in persons with pancreatic cancer, there is limited knowledge about the expression patterns and prognostic consequences of genes connected to zinc homeostasis in pancreatic cancer.

Existing studies have identified a connection between expression level of SLC39A6 and tumor size, along with lymph infiltration. A previous research has demonstrated the relationship of the SLC39A6 and pancreatic cancer by creating a nude mice model with down-regulated SLC39A6 expression. This research revealed that blocking SLC39A6 could effectively impede the growth and spreading of pancreatic cancer cells both in vivo and in vitro experiments. These findings demonstrate the correlation between SLC39A6 expression and pancreatic cancer cell proliferation. It is suggested that targeting SLC39A6 could significantly reduce both metastasis and proliferation of pancreatic cancer cells[46,47]. By deepening the research in this direction, artificially down-regulated the SLC39A6 expression

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to lead lysozincrosis to reduce both metastasis and proliferation of pancreatic cancer cells could be a potential approach in pancreatic cancer treatment or reduce recurrence.

Compared to the normal pancreatic control group, there was an increase in the expression levels of ZIP1, ZIP3, ZIP4, ZIP7, ZIP9, ZIP10, ZIP11, ZIP13, ZnT1, ZnT5, ZnT6, ZnT7, and ZnT9, whereas the expression levels of ZIP5, ZIP14, ZnT2, MT1G, MT1H, and MT1X were found to decrease. Notably, higher expression of ZIP4, ZIP11, ZnT1, or ZnT6 indicates a poor prognosis. The aforementioned findings hint at potential involvement of PAAD patients in different cancer-related processes and pathways, which can be linked to the differentially expressed genes relevant to zinc homeostasis[46]. By detecting the above mentioned biomarkers to differentiate from normal pancreatic tissue to pancreatic cancer, it may lead to take effective approaches to provide better prognosis for pancreatic cancer patients to increase five years survival rate of pancreatic cancer.

As an essential metal ion and nutrient, zinc plays a crucial role in cellular function. Disruptions in zinc homeostasis have been linked to mechanisms of cell death and the development of chemoresistance in pancreatic cancer. A recent study revealed that circular RNA ANAPC7 has inhibitory effects on pancreatic cancer growth by sequestering miR-373 and improving the overall disease condition. The study identified PHLPP2 as a new target gene of miR-373 in pancreatic cancer as it regulates AKT signal transduction. PHLPP2, a protein phosphatase, impedes CREB phosphorylation, a zinc-dependent transcription factor monitored by ZIP4, thereby promoting miR-373 expression through transcriptional regulation. This investigation revealed a previously unknown feedforward cycle involving CREB, miR-373, and PHLPP2 in the signaling axis mediated by ZIP4 in pancreatic cancer.

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Furthermore, the study discovered that circANAPC7 lowers TGF-β expression and secretion via STAT5-β, effectively reversing muscle atrophy induced by ZIP4 and improving the overall prognosis of the disease[48]. It showed the crucial influence of ZIP4 in lysozincrosis and the unique connection between pancreatic cancer and lysozincrosis, guiding the direction of further research of combination of lysocrosis and pancreatic cancer treatment.

ZIP4, key zinc transporter, is upregulated in pancreatic cancer. Overexpression of ZIP4 triggers activation of the IL6/STAT3 pathway, leading to increased expression of VEGF and MMP2. However, the specific mechanism by which the activation of downstream signaling pathways enhances migration and invasion in pancreatic cancer is unclear[46]. In view of the particularity of lysozincrosis, the application of lysozincrosis in the treatment of pancreatic cancer may need further research, but it inspired a new way to help diagnose early pancreatic cancer and prognosis of pancreatic cancer by measuring zinc transporter.

5 Discussion

Ferroptosis is a unique programmed cell death with specific metabolic pathways that provide insights into its induction. Iron overload is a fundamental trigger for ferroptosis, leading to a cascade of polyunsaturated fatty acids undergo peroxidation. This accumulation of toxic intracellular reactive oxygen species (ROS) ultimately leads to cell death[14]. Notably, cells undergoing ferroptosis exhibit elevated levels of iron and ROS in comparison to normal cells, emphasizing the pivotal role of iron in this process. The destructive impact of lipid peroxidation on the integrity of cellular membranes adversely affects diverse organelles. Among them, mitochondria are particularly susceptible and show significant changes relative to other organelles. Deciphering the interconnected metabolic pathways associated with

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ferroptosis provides insights into inducing and inhibiting this process through targeted interventions.

Significant advances in ferroptosis research suggest that practical application of ferroptosis-based treatments for pancreatic cancer is imminent. Pancreatic cancer presents distinctive challenges due to its susceptibility to drug resistance when compared to other cancers[7]. Mutations in pancreatic cancer cells enhance their susceptibility to ferroptosis. Given the connections and reliance of pancreatic cancer cells on specific components, the targeting of ferroptosis exhibits potential to become a novel therapy by inducing cell death and overcome drug resistance during pancreatic cancer treatment .

Nevertheless, due to the relationship between ferroptosis and immunity, there are challenges in using ferroptosis for pancreatic cancer treatment. The impact of ferroptosis on immunity primarily occurs within the tumor microenvironment. It is important to pay caution as the release of damage-associated molecular patterns (DAMPs) from dying cells containing iron can affect the polarization of macrophages in the tumor microenvironment towards the M2 subtype, exacerbating the condition of pancreatic cancer[27]. This effect is not limited to macrophages, but also extends to T cells. It has been demonstrated that the activity and function of CD8+ T cells and CD4+ T cells are influenced by lipid peroxidation and ferroptosis. Additionally, the activation of CD8+ T cells down-regulates the expression of system xc− which reduce the uptake of cystine by cancer cells, thereby reducing GSH in cancer cells and improving the sensitivity of cells to ferroptosis. This effect of ferroptosis on T cells may also could be utilized in pancreatic cancer treatment in the future but more in-depth research is still needed. Therefore, it is crucial to consider the potential pathological

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implications of ferroptosis in the treatment of pancreatic cancer as it may contribute to the malignant progression of the disease. Moreover, while it is possible to induce ferroptosis in pancreatic cancer cells according to their unique connections, it is unclear if this method may cause harm to healthy cells or have negative impacts on patients. It highlights the complex and diverse biological impacts of ferroptosis in the treatment of pancreatic cancer. This underscores the importance of a comprehensive understanding when utilizing ferroptosis as a therapeutic approach in the future.

Before considering ferroptosis induction as a viable cancer treatment approach, it is crucial to address these concerns and investigate potential solutions. Moreover, if the aforementioned obstacles can be overcome, it begs the inquiry of whether inducing ferroptosis for pancreatic cancer treatment can be extended to other domains. By exploring the correlation between other cancer types and ferroptosis, insights and approaches for addressing cancer-related problems may be obtained. Furthermore, the investigation of ferroptosis could yield insights into other metal-related forms of cell death, potentially paving the way for further research and advancements in related fields.

Copper and zinc are essential cofactors for enzymes throughout the organism. They exhibit a dual nature, exerting their function at moderate intracellular concentrations while causing toxicity and lead to cell death at high intracellular concentrations.

Genetic variations in copper homeostasis contribute to severe and potentially life-threatening diseases. Additionally, agents involved in copper ion transport and chelation are acknowledged as potential anticancer therapeutics[49]. The accumulation of copper and elevation of fatty acylated proteins are key factors in regulating cuproptosis[50]. Disruptions

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in copper homeostasis can influence cancer cell migration and proliferation, promoting tumor growth. When cuproptosis or similar apoptotic process inspired from cuproptosis is used in cancer treatment with further researches of cuproptosis have been done, it is necessary to consider the efficacy and the risk to normal tissues and cells by cuproptosis. Certain cancers with increased mitochondrial metabolism, tumors containing stem cell-like cells, and drug-resistant cancers are expected to display more positive responses to these treatments. Proteasome inhibitors have demonstrated the ability to induce elevated mitochondrial metabolic states in cells. In addition, the use of copper ion carriers for tumor treatment provides a promising avenue for future applications.

The recently discovered lysozincrosis, a distinct type of regulatory cell death, offers potential in cancer and disease research. ZIP4, a key protein, playing a significant role in cell proliferation, metastasis, drug resistance, and pancreatic cancer-related cachexia, is a crucial role to find out the deeper connection between pancreatic cancer and lysozincrosis. Down-regulating lysozincrosis gene expression as SCL39A6 to intervene pancreatic cancer exacerbate is a promising direction. To explore the complex interplay between zinc and cancer metabolism, especially in relation to tumor initiation, growth, metastasis, stem cell habitats, and inflammatory responses, further research into nutritional zinc sensing is crucial. Utilizing methodologies such as advanced sequencing, proteomics, metabolomics, and other analytical tools promises to reveal new understandings of metal biology in relation to cancer and other illnesses.

Nowadays, with the further study of metal-related cell death, more metal-related cell death have been found. Calcicoptosis is a new form of metal-related cell death which has

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great potential in the treatment of pancreatic cancer. Calcium participates in normal physiological activities in cells, but excessive calcium can lead to mitochondrial damage and other cellular pathologies which is called calcicoptosis. In the tumor environment, it may lead to the increase of intracellular calcium content in cancer cells. At the same time, radiotherapy and chemotherapy may also increase intracellular calcium levels. If more in-depth research can be carried out on calcicoptosis, it may also become an effective method for the treatment of pancreatic cancer in the future. There may also be great research prospects for other undetected or poorly studied metal-related cell deaths.

Finally, a table of metal death and its activators is added to help understand and help future research in the field(**Table 1**).

6 Conclusion

This review explores the intrinsic characteristics of pancreatic cancer and associated treatment challenges objectively. It discusses three separate forms of metal-related cell death, highlighting their potential as adjunctive therapies for pancreatic cancer treatment due to their unique characteristics, pathways, and connections with the disease, which make their association with pancreatic cancer especially remarkable since they affect different aspects of the disease. By utilizing these distinct traits, this review endeavors to provide innovative insights and strategies for future treatments of pancreatic cancer. Pancreatic cancer cells have higher level of iron ion, phosphate hydroperoxides, and glutathione, which make it be highly sensitive to ferroptosis. Therefore, ferroptosis has more feasibility in diagnosis, treatment and prognosis of pancreatic cancer. Cuproptosis is a process due to the accumulation of copper ion along with the reduction of Fe-S cluster proteins, resulting in cell death. Recently studies

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exposed the potential of cuproptosis use for pancreatic cancer treatment. But lysozincrosis still require further in-depth research to be put in use. However, it is essential to acknowledge that the implementation of these three types of metal-related cell death as a treatment may have adverse effects on the body, making it a double-edged sword in the pancreatic cancer treatment. Therefore, comprehensive research dedicated to this topic is crucial to address these potential challenges. Mitigating the adverse effects linked with metal-related cell death in clinical applications is a crucial aspect for future translational efforts. The successful exploration of metal-related cell death as a therapeutic approach for pancreatic cancer could have implications that extend beyond this specific field.

Declarations:

Consent for publication:

Not applicable

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest statement:

The authors declare no conflicting financial interests.

Authors' contributions:

SJ Dai, HW Sun and HR Kong designed the review and supervised the review. SJ Dai, ZM Chen, CC Wang, Y Ja, TT Liu, K Lin, LY Huang, CQ Ren and SY Zhou participated in writing manuscript.

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Data availability statement:

No data was used for the research described in the article. None of data associated with the review has been deposited into a publicly available repository.

FIGURE AND TABLE LEGENDS

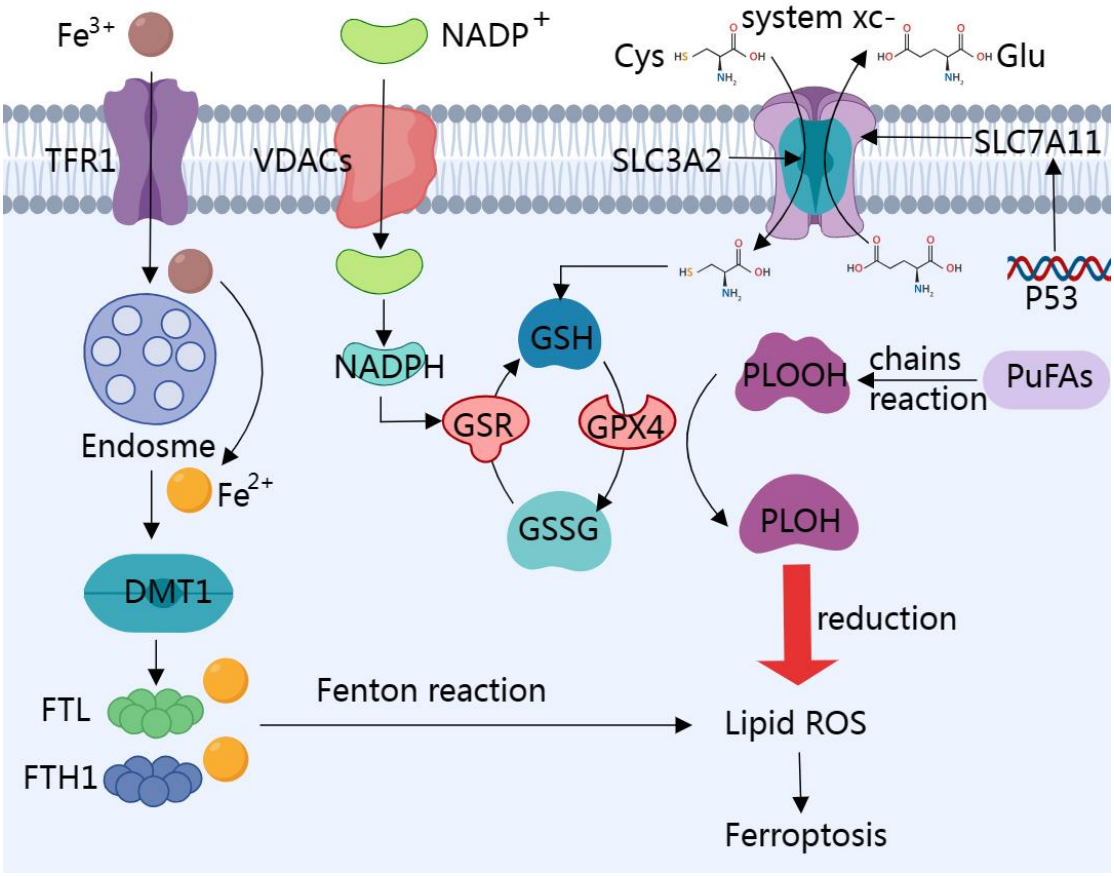

Figure 1. Main pathways and metabolic pathways of ferroptosis.

Fe^{3+} enter cells through a series of transporters and catalyze lipid peroxidation via the Fenton reaction, leading to ferroptosis. System Xc- transports cysteine into cells while exporting glutamic acid, with the critical subunit SCL7A11 being regulated by the P53 gene. Cys is transformed into GSH within cells, and GPX4 facilitates the conversion of GSH into GSSG, while PLOOH, which is harmful, is converted into harmless PLOH. GSR helps GSSG undergo retransformation into GSH, and VDACs provide NADPH crucial to this process. Such a process effectively inhibits cell ferroptosis.

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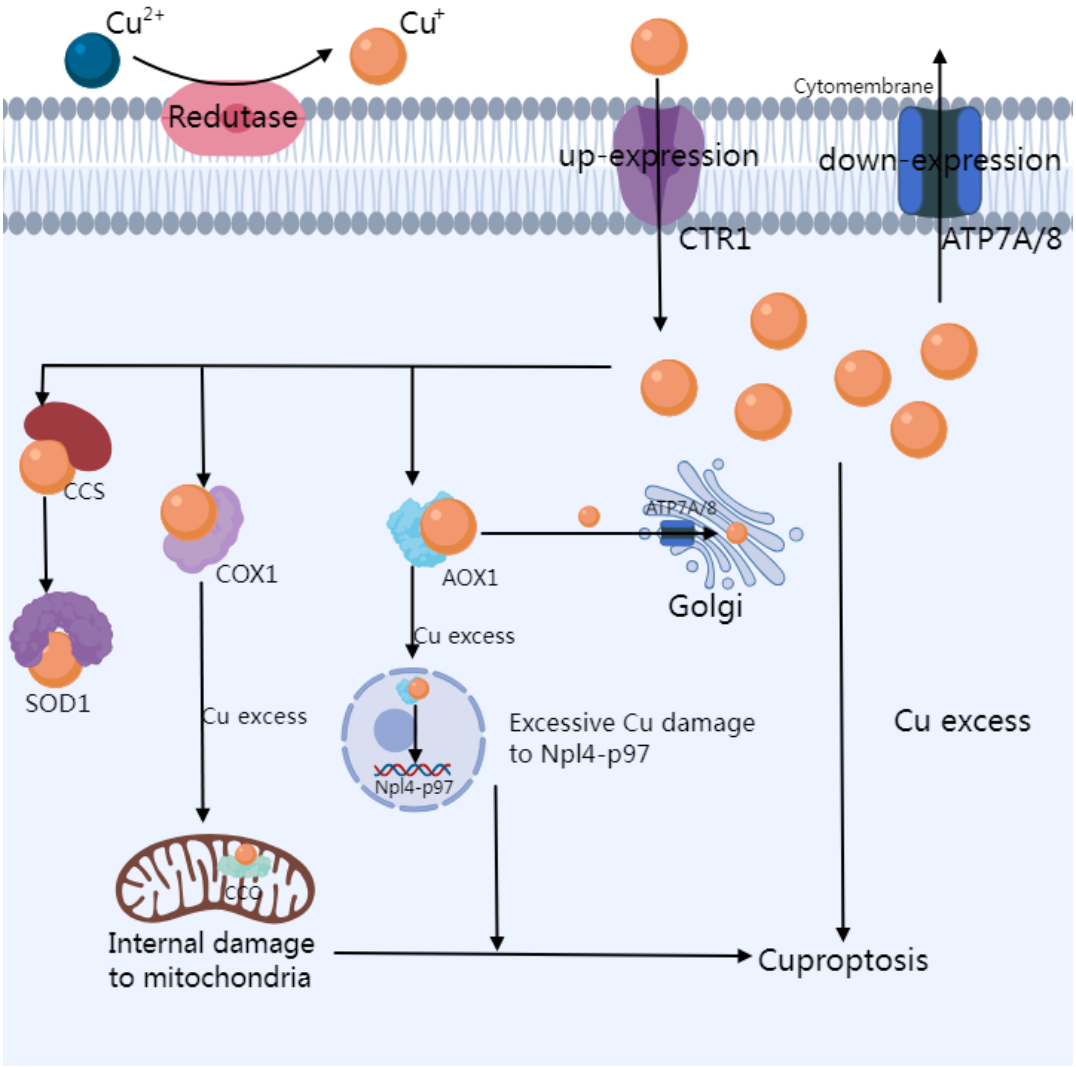

Figure 2. Main pathways and metabolic pathways of cuproptosis.

Excessive copper could directly lead to cuproptosis. Excessive copper entering mitochondria disrupts Fe-S cluster proteins, leading to mitochondrial damage and ultimately triggering cuproptosis. Excessive copper in the nucleus disrupts the Npl4-p97 pathway, leading to proteotoxic stress and cuproptosis.

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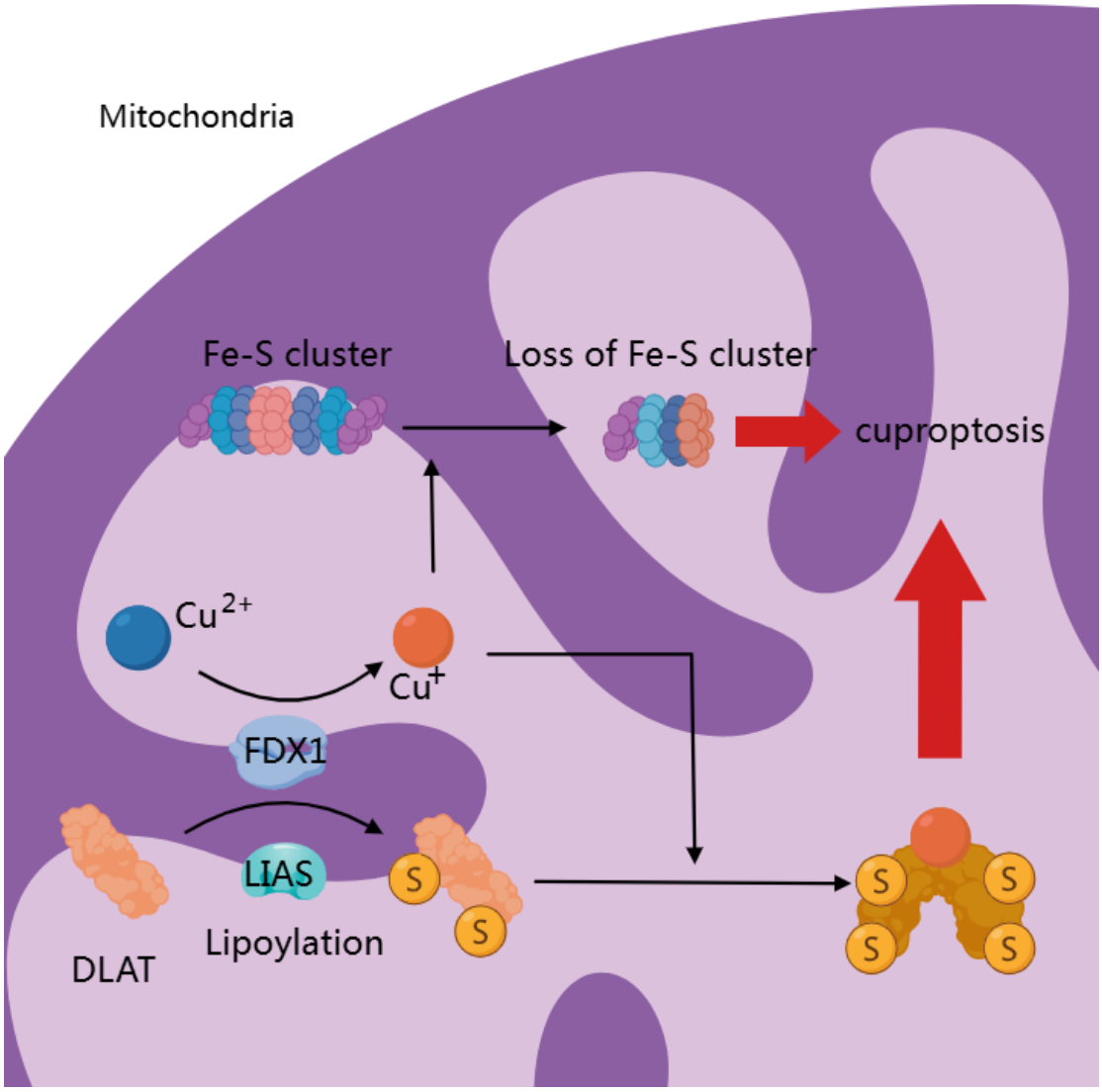

Figure 3. The relationship between Fe-S cluster proteins and cuproptosis.

With the plethora of intracellular concentration of Cu^{2+} excessive Cu^{2+} binds to DLAT, inducing abnormal oligomerization of DLAT. The increase of insoluble DLAT leads to cytotoxicity and induces cell death. Meanwhile, FDX1 transform Cu^{2+} to Cu^{+}, leading to inhibition of Fe-S cluster protein synthesis and a decrease in intracellular Fe-S cluster proteins, resulting in cell death.

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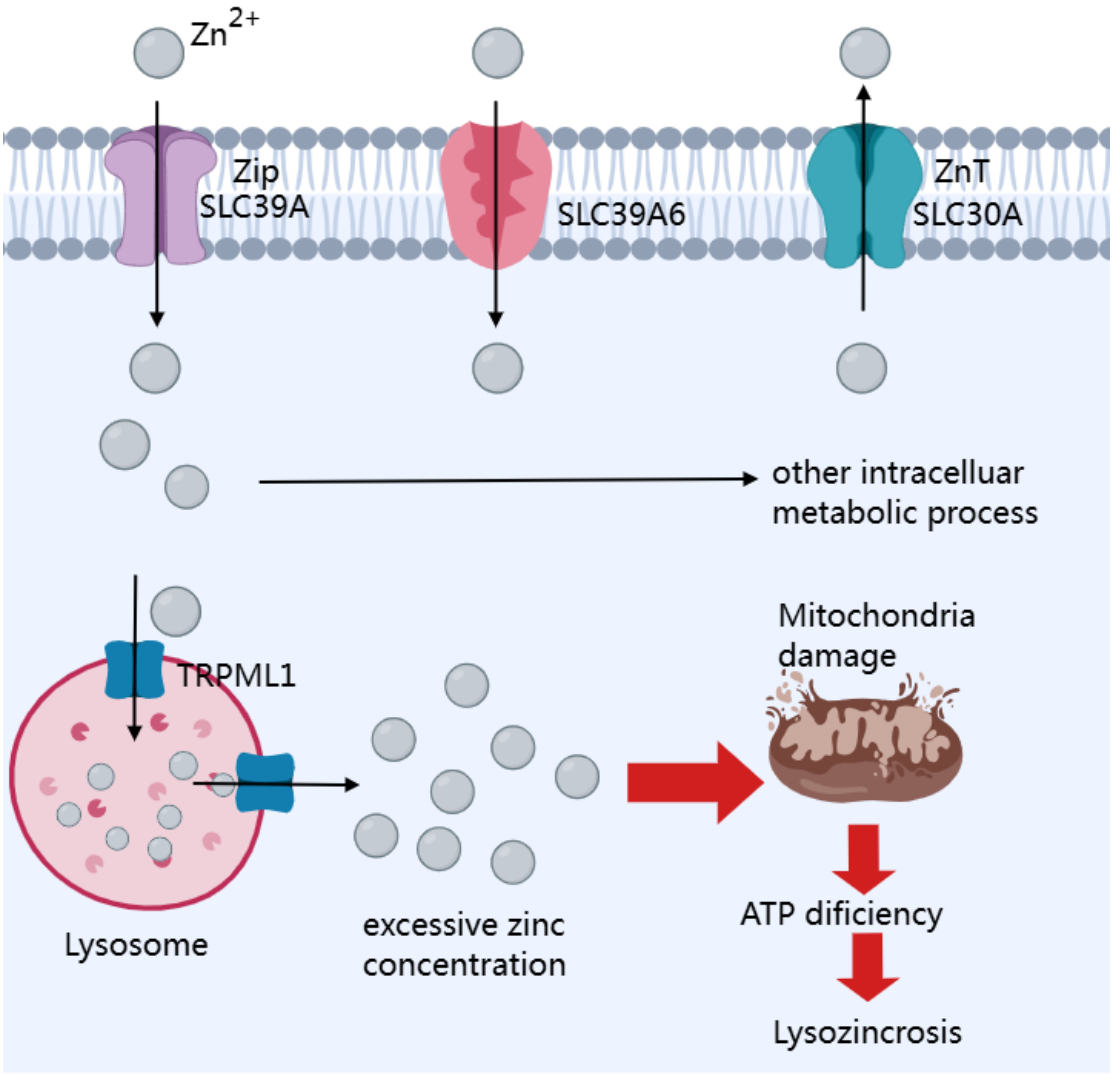

Figure 4. Main pathways and metabolic pathways of lysozincrosis.

The SLC39A and SLC30A families are two zinc transporter families discovered in mammals that respectively regulate the transport of zinc ions inside and outside of cells. The SLC39A6 protein is primarily located in the cell membrane and transports zinc ions from the extracellular layer, or organelles to the cytoplasm. The expression of SLC39A6 is associated with pancreatic cancer proliferation. Inhibiting SLC39A6 significantly decreases the metastasis and proliferation of pancreatic cancer cells.

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Table 1

Table 1. Activators of metal-related cell death mentioned

Metal-related death	Direct activator	Indirect activator
Ferroptosis	Fe	AA, AdA, Erastin
Cuproptosis	Cu, Fatty acylation proteins	Thioacylated proteins
Lysozincrosis	Zn	

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