

Research progress of pancreatic cancer based on ferroptosis-cuproptosis interaction (Review)

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Abstract. Pancreatic cancer is a highly aggressive malignancy with a poor prognosis and pancreatic ductal adenocarcinoma (PDAC) constitutes the overwhelming majority of histological subtypes. KRAS mutation-driven metabolic reprogramming renders PDAC highly dependent on metal ion homeostasis and antioxidant systems, thereby providing a novel rationale for therapeutic strategies targeting ferroptosis and cuproptosis. Ferroptosis is a form of regulated cell death caused by the excessive accumulation of iron-dependent lipid peroxidation, whereas cuproptosis is a newly characterised mode of cell death triggered by copper binding to mitochondrial lipoylated proteins, leading to proteotoxic stress. In PDAC, these two forms of cell death are not independent; rather, they interact through multiple metabolic and stress-response pathways. This review systematically summarizes the core molecular mechanisms of ferroptosis and cuproptosis, with particular emphasis on their crosstalk mediated by key nodes, including glutathione, mitochondria, the tricarboxylic acid cycle, iron-sulfur clusters and glutathione peroxidase 4. It further analyses how tumour microenvironmental factors, such as KRAS mutation, cancer-associated fibroblasts, hypoxia and epithelial-mesenchymal transition, regulate these two death programmes, and discusses their functional significance in drug resistance, cancer stem cells and the immune microenvironment. Finally,

this review outlines PDAC therapeutic strategies based on the coordinated regulation of ferroptosis and cuproptosis, with the aim of providing a theoretical basis for the development of novel synergistic therapies targeting metal-dependent cell death in pancreatic cancer.

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1. Introduction

Pancreatic cancer is a highly malignant tumour of the digestive system with a poor prognosis and its incidence closely parallels its mortality. Globally, pancreatic cancer ranks 12th in incidence among all malignancies, accounting for 2.6% of all cancer cases and 6th in cancer-related mortality, accounting for 4.8% of all cancer deaths (1). Pancreatic ductal adenocarcinoma (PDAC) comprises the vast majority of the histological subtypes of pancreatic cancer and is characterised by an insidious clinical onset, abundant stromal desmoplasia, poor vascularisation, marked hypoxia and broad resistance to conventional chemotherapy and immunotherapy. PDAC is further characterised by profound metabolic reprogramming, a dense immunosuppressive microenvironment and extensive therapeutic resistance; consequently, the efficacy of conventional chemotherapy, targeted therapy and immunotherapy remains limited, underscoring the urgent need to develop novel therapeutic strategies from the perspectives of cell death regulation and metabolic vulnerabilities (2). At the molecular level, KRAS mutation is one of the most fundamental driver events in PDAC, and large cohort studies have shown that nearly all PDAC cases harbour mutations in exon 2 of KRAS. The coexistence of KRAS-driven metabolic

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reprogramming, elevated reactive oxygen species (ROS) and nutrient competition renders PDAC cells highly dependent on metal ion homeostasis and antioxidant systems for survival, thereby providing a critical entry point for the investigation of ferroptosis and cuproptosis.

Ferroptosis was first defined in 2012 and is characterised by the excessive accumulation of iron-dependent lipid peroxidation within cellular membranes (3). Subsequently, Yang *et al* (4) demonstrated that glutathione (GSH) peroxidase 4 (GPX4) is a key suppressor of ferroptosis. Later studies further established that the ferroptosis suppressor protein 1 (FSP1)-coenzyme Q10 (CoQ10) pathway and the dihydroorotate dehydrogenase-mitochondrial CoQ pathway are important anti-ferroptotic defence mechanisms independent of GPX4 (5,6). Cuproptosis, a novel form of regulated cell death, was first proposed by Tsvetkov *et al* (7) in 2022. That study demonstrated that copper ions do not exert toxicity through non-oxidative stress; rather, they selectively target lipoylated proteins in the mitochondrial tricarboxylic acid (TCA) cycle, inducing the aberrant aggregation of proteins such as dihydrolipoamide S-acetyltransferase (DLAT) and dihydrolipoamide S-succinyltransferase (DLST), the degradation of iron-sulfur (Fe-S) proteins and acute proteotoxic stress. This molecular mechanism is clearly distinct from apoptosis, necroptosis and ferroptosis.

In PDAC, the importance of investigating ferroptosis and cuproptosis extends beyond determining whether these can directly eliminate tumour cells. More importantly, such investigation may help to address several key scientific questions: Why PDAC can persist in a microenvironment characterised by high oxidative stress; why certain therapeutic interventions paradoxically induce drug resistance, maintain tumour stemness or even promote inflammation-associated tumour progression; and how shared regulatory nodes between these two cell death pathways may be exploited to achieve coordinated intervention against KRAS-driven metabolic reprogramming, cancer-associated fibroblast (CAF)-mediated stromal support, hypoxia-mediated protection and stem cell-like tumour phenotypes (8). This review systematically summarises the core mechanisms and pathways of ferroptosis and cuproptosis in pancreatic cancer (Table I).

2. Molecular mechanisms of ferroptosis and cuproptosis

Molecular mechanisms of ferroptosis and its unique features in PDAC. The regulatory network of ferroptosis primarily functions through the coordinated action of three core pathways. First, system x_c⁻, with solute carrier family 7 member 11 (SLC7A11) as its key component, mediates the uptake of cystine into cells, where it is subsequently reduced to cysteine and serves as an essential substrate for intracellular GSH synthesis (9). Second, GPX4 uses GSH as a cofactor to continuously detoxify intracellular lipid peroxides, thereby maintaining redox homeostasis. Meanwhile, lipid metabolism-related enzymes, such as acyl-CoA synthetase long-chain family member 4 (ACSL4), determine membrane susceptibility to lipid peroxidation by regulating the abundance of polyunsaturated fatty acids in membrane phospholipids (10). In addition, FSP1 reduces CoQ10 at the plasma membrane to

block the chain propagation of lipid radicals, whereas DHODH provides another independent anti-ferroptotic defense mechanism at the inner mitochondrial membrane; together, these pathways constitute an integrated regulatory system governing ferroptosis (9,11).

In PDAC, ferroptosis is not merely a conventional cell death phenomenon but is closely linked to tumour metabolic addiction. Once inside the cell, cystine is primarily used for the synthesis of GSH and coenzyme A, both of which jointly determine the threshold for ferroptosis induction. Genetic deletion of SLC7A11 or systemic depletion of cystine and cysteine using cyst(e)inase can selectively induce ferroptosis in pancreatic tumours *in vivo* and effectively suppress PDAC growth. Furthermore, inhibition of glutamic-oxaloacetic transaminase 1 (GOT1) can further sensitise PDAC cells to strategies involving blockade of cystine uptake, inhibition of GSH synthesis or direct targeting of GPX4 by inducing redox imbalance, disrupting mitochondrial metabolism, promoting ferritinophagy and increasing the release of labile iron, thereby facilitating ferroptosis (9).

PDAC has also evolved multilayered defence networks against ferroptosis. Heat shock protein family A member 5 (HSPA5) stabilises GPX4 and negatively regulates ferroptosis, thereby attenuating the cytotoxic effect of gemcitabine (12). High mobility group AT-hook 2 enhances GPX4 translation through activation of mammalian target of rapamycin complex 1, thereby reducing the sensitivity of PDAC cells to ferroptosis-inducing agents such as RAS-selective lethal 3 or gemcitabine-based combination therapy (13). Signal transducer and activator of transcription 3 (STAT3) can directly bind to the GPX4 promoter and enhance its transcription, whereas thiostrepton can induce ferroptosis by inhibiting the STAT3-GPX4 axis (14). Nuclear factor erythroid 2-like 2 (NFE2L2/NRF2) upregulates the transcription of microsomal GSH S-transferase 1 (MGST1). MGST1 binds to arachidonate 5-lipoxygenase (ALOX5), thereby inhibiting associated lipid peroxidation and diminishing the sensitivity of PDAC cells to ferroptosis (15).

Molecular mechanisms of cuproptosis and its unique features in PDAC. During cellular copper uptake, oxidised copper is first reduced by six-transmembrane epithelial antigen of the prostate and then transported into the cell via high-affinity copper transporter 1 (CTR1) (16-18).

The core mechanism of cuproptosis lies not in non-specific oxidative stress caused by copper overload, but rather in the specific interaction between copper and mitochondrial lipoylated proteins. Tsvetkov *et al* (7) found that copper toxicity depends on mitochondrial respiration and TCA cycle activity, with ferredoxin 1 (FDX1) acting upstream to regulate protein lipoylation. Upon copper accumulation, copper ions can directly bind to lipoylated proteins such as DLAT, triggering the aggregation of lipoylated proteins, the loss of Fe-S cluster proteins and the upregulation of HSP70, ultimately leading to proteotoxic stress and cell death. Accordingly, cuproptosis is more likely to occur in cell populations with active oxidative phosphorylation (OXPHOS) and high levels of protein lipoylation (7).

Clinical studies have demonstrated that copper levels are significantly elevated in the serum and tissues of patients with

Table I. Core mechanisms and pathways of ferroptosis and cuproptosis in pancreatic cancer cells.

Core mechanisms or pathways	Key factors	Functional outcomes and research significance	(Refs.)
Cystine-GSH-GPX4 antioxidant axis	SLC7A11, GSH, GPX4	Scavenging of lipid peroxides and inhibition of ferroptosis	(9)
FSP1/DHODH-CoQ anti-ferroptosis pathway	FSP1, DHODH, CoQ10	Inhibition of lipid peroxidation independently of GPX4	(5,6)
Lipid metabolic remodeling pathway	ACSL4	Enhancement of the oxidative sensitivity of membrane phospholipids and promotion of ferroptosis	(10)
Copper uptake-mitochondrial accumulation pathway	CTR1	Elevation of intracellular copper levels and facilitation of cuproptosis	(7,18)
Lipoylated protein toxicity pathway	FDX1, LIAS, DLAT, DLST	Copper binds lipoylated proteins to induce aggregation and protein toxicity	(7)
Fe-S cluster homoeostasis interactive pathway	NFS1, IRP1, Fe-S proteins	Degradation of Fe-S proteins triggers metabolic collapse	(39-41)
Mitochondrial GSH buffering pathway	SLC25A39, mitochondrial GSH	Chelation of Cu ⁺ and reduction of copper toxicity	(22)
GSH shared hub pathway	GSH, NRF2	GSH resists both ferroptosis and cuproptosis with distinct mechanisms	(25,26)
Mitochondria-TCA cycle crosstalk	TCA cycle, OXPHOS	Metabolic status determines the preference of cell death mode	(31)
Direct crosstalk pathway of GPX4	Cu ²⁺ , GPX4, TAX1BP1	Copper induces autophagic degradation of GPX4 and amplifies ferroptosis	(43)

SLC7A11, solute carrier family 7 member 11; GSH, glutathione; GPX4, glutathione peroxidase 4; FSP1, ferroptosis suppressor protein 1; DHODH, dihydroorotate dehydrogenase; CoQ10, coenzyme Q10; ACSL4, acyl-CoA synthetase long chain family member 4; CTR1, copper transporter 1; FDX1, ferredoxin 1; LIAS, lipid acid synthase; DLAT, dihydrolipoyl transacetylase; DLST, dihydrolipoamide S-succinyltransferase; NFS1, nitrogen fixation S 1 homolog; IRP1, iron regulatory protein 1; Fe-S, iron-sulfur; SLC25A39, solute carrier family 25 member 39; NRF2, nuclear factor erythroid 2-related factor 2; TCA, tricarboxylic acid; OXPHOS, oxidative phosphorylation; TAX1BP1, tax1 binding protein 1.

pancreatic cancer (19). Pancreatic cancer cells increase copper uptake and accumulation by upregulating copper transporters such as CTR1, thereby promoting cellular proliferation and survival (20). In addition, copper serves as a cofactor for multiple key enzymes and is involved in various physiological processes in PDAC cells.

Compared with ferroptosis, direct mechanistic studies of cuproptosis in PDAC began relatively late; however, several important advances have already been made. A mechanistic study published in 2024 showed that the elesclomol-copper complex (ES-Cu) can stabilise NFE2L2 protein and enhance its activity in PDAC cells. However, unlike erastin-induced ferroptosis, ES-Cu preferentially induces the expression of glutamate-cysteine ligase regulatory subunit (GCLM) and glutamate-cysteine ligase catalytic subunit (GCLC), rather than that of genes such as SLC7A11 and GPX4. At the same time, SLC25A39 mediates mitochondrial GSH import (21), and loss of SLC25A39 decreases mitochondrial GSH levels while increasing mitochondrial Cu⁺ concentrations, thereby significantly enhancing ES-Cu-induced cuproptosis. These findings indicate that mitochondrial GSH suppresses cuproptosis not by scavenging lipid peroxidation, but by reducing copper toxicity through copper buffering or chelation (22).

Studies further indicated that ES alone has limited efficacy, whereas, in combination with a copper source, it can

significantly and irreversibly attenuate the cancer stem cell (CSC) phenotype in both human and murine PDAC models. The underlying mechanisms include a 2- to 4-fold increase in intracellular copper levels, depletion of Fe-S cluster proteins, accumulation of mitochondrial lipoylated DLAT and inhibition of the copper-dependent antioxidant enzyme superoxide dismutase 1 (7). More importantly, this strategy improves the efficacy of gemcitabine in immunocompetent PDAC models, suggesting that cuproptosis may hold unique therapeutic value against tumour subpopulations characterised by stemness, drug resistance and heightened mitochondrial metabolism (23).

Although existing studies have preliminarily elucidated the regulatory mechanisms and therapeutic potential of ferroptosis in PDAC, several limitations continue to restrict in-depth mechanistic investigation and clinical translation. First, most current studies focus on the independent regulatory effects of a single molecule or pathway, whereas the crosstalk and compensatory mechanisms among various anti-ferroptosis pathways remain elusive. Second, most existing conclusions are derived from *in vitro* cell experiments and conventional *in vivo* animal models, with limited validation in clinically relevant models such as patient-derived organoids and orthotopic xenograft tumours. Furthermore, the effects of the unique desmoplastic microenvironment and hypoxic stress in PDAC on ferroptosis sensitivity and related pathway activity have been largely

overlooked, leading to discrepancies between experimental findings and authentic clinical pathological conditions and thereby limiting their clinical relevance.

3. Nodes of crosstalk between ferroptosis and cuproptosis in PDAC

In PDAC, ferroptosis and cuproptosis are not independent forms of cell death. Multiple overlapping pathways and key molecules jointly mediate these two death modalities, thereby constructing an intricate network of interacting nodes (Fig. 1).

GSH: The most important shared hub of the two death programs. GSH is not only a major intracellular reductant but also an essential cofactor for GPX4 (24). GSH represents the primary node linking ferroptosis and cuproptosis, although its mechanistic roles differ between these two forms of cell death. In ferroptosis models, GSH primarily functions as the reducing substrate for GPX4; depletion of cysteine or GSH directly compromises the ability of GPX4 to eliminate membrane lipid peroxides, thereby promoting ferroptotic execution. In cuproptosis models, GSH, particularly mitochondrial GSH, appears to function primarily as a buffer or chelator of Cu^+ , thereby reducing mitochondrial copper toxicity. In brief, GSH is mainly involved in lipid peroxide detoxification during ferroptosis, whereas in cuproptosis, it acts predominantly as a copper-ion buffer. This is currently one of the most direct and convincing nodes of ferroptosis-cuproptosis crosstalk identified in PDAC (9).

Further study has shown that NFE2L2/NRF2 is not merely a broad-spectrum antioxidant transcription factor, but instead differentially regulates downstream target-gene expression according to the type of death-related stress encountered by the cell (22). In PDAC, when cells are exposed to cuproptosis-inducing stimuli, NRF2 preferentially upregulates GCLM and GCLC to drive GSH biosynthesis; under ferroptotic stress, by contrast, it preferentially activates canonical antioxidant target genes such as SLC7A11. This feature indicates that a single transcription factor can specifically sense two distinct stress signals-copper overload and disordered iron metabolism- and subsequently orchestrate different adaptive response programmes. In normal pancreatic tissues, transient NRF2 activation exerts a protective effect. By contrast, sustained excessive NRF2 activation acts as a damaging factor in models with permanent autophagy deficiency, aggravating endoplasmic reticulum stress, apoptosis and chronic inflammatory lesions (25,26). These observations suggest that indiscriminate, broad inhibition of global NRF2 activity is unlikely to achieve optimal antitumour efficacy. Compared with coarse blockade of the entire antioxidant network, a more precise strategy targeting NRF2 downstream branches-including GSH synthesis, mitochondrial GSH transport and GPX4-mediated lipid antioxidant defense-may more effectively disrupt the metabolic adaptation barrier of tumour cells and provide a more specific therapeutic framework for PDAC.

Mitochondria: The cellular site of interaction between the two death programs. As the central hub of cellular energy metabolism, mitochondria are not only the principal site of ATP

generation but also key organelles involved in ROS production, regulation of iron metabolism and integration of multiple cell-death signals. At the mitochondrial level, ferroptosis and cuproptosis in PDAC exhibit clear crosstalk: Mitochondria are both an important source of lipid peroxidation and a regulatory centre for iron metabolism, while also serving as the site of copper-dependent proteotoxic stress. Further studies have confirmed that mitochondria not only generate ROS through the electron transport chain and thereby drive lipid peroxidation, but that their intrinsic lipid composition, metabolic state and Fe-S cluster homeostasis also directly determine cellular sensitivity to ferroptosis (27,28).

Mitochondria exert particularly important regulatory effects on ferroptosis in PDAC cells. Work from Kremer *et al* (11), based on experiments involving GOT1 inhibition, has provided robust mechanistic insight. Impaired mitochondrial metabolism sensitises pancreatic cancer cells to ferroptosis via two independent pathways. On the one hand, cellular redox homeostasis is disrupted, accompanied by a reduced NADPH/NADP⁺ ratio, which compromises GPX4-dependent clearance of lipid peroxides. On the other hand, ferritinophagy is activated, releasing stored iron into the intracellular labile iron pool and amplifying oxidative damage driven by the Fenton reaction (11). This finding establishes a direct mechanistic link between mitochondrial metabolism and ferroptosis. Accordingly, mitochondrial function extends far beyond ROS production; it also acts as a pivotal metabolic checkpoint that governs ferroptosis responsiveness in tumour cells.

At the same time, copper ions preferentially target lipoylated proteins within the mitochondrial matrix, particularly key enzymes of the TCA cycle, such as DLAT and DLST (7). Lipoylation is a highly conserved post-translational modification in which the substrate lipoic acid is synthesized *de novo* in mitochondria by lipoic acid synthase (LIAS) and then transferred to specific lysine residues by lipoyltransferase 1 (LIPT1) and LIPT2 (29). In mammalian cells, lipoylation occurs mainly on four mitochondrial enzyme-complex subunits: DLAT, DLST, dihydrolipoamide branched-chain transacylase E2 and glycine cleavage system protein H (29,30). These proteins are all core components of the TCA cycle or related metabolic pathways, and their lipoylation status directly determines the catalytic activity of the respective enzyme complexes and the overall metabolic capacity of mitochondria. Upon binding to the lipoyl moieties of these proteins, copper can induce protein aggregation, loss of Fe-S cluster proteins and proteotoxic stress, ultimately resulting in cell death. Importantly, this process is highly dependent on mitochondrial respiration and TCA cycle activity; mitochondrial GSH imported via SLC25A39 directly chelates Cu^+ to counteract cuproptosis. Tumour cells with higher mitochondrial metabolic activity exhibit greater sensitivity to cuproptosis (7,31).

Thus, mitochondrial metabolic status in PDAC contributes to shaping the dynamic balance between ferroptosis and cuproptosis. Upon mitochondrial metabolic suppression and reduced OXPHOS activity, cells may display an increased propensity for ferroptosis accompanied by ferritinophagy activation and redox imbalance. By contrast, cells tend to become more vulnerable to copper-triggered protein aggregation when mitochondrial TCA-cycle activity is high and

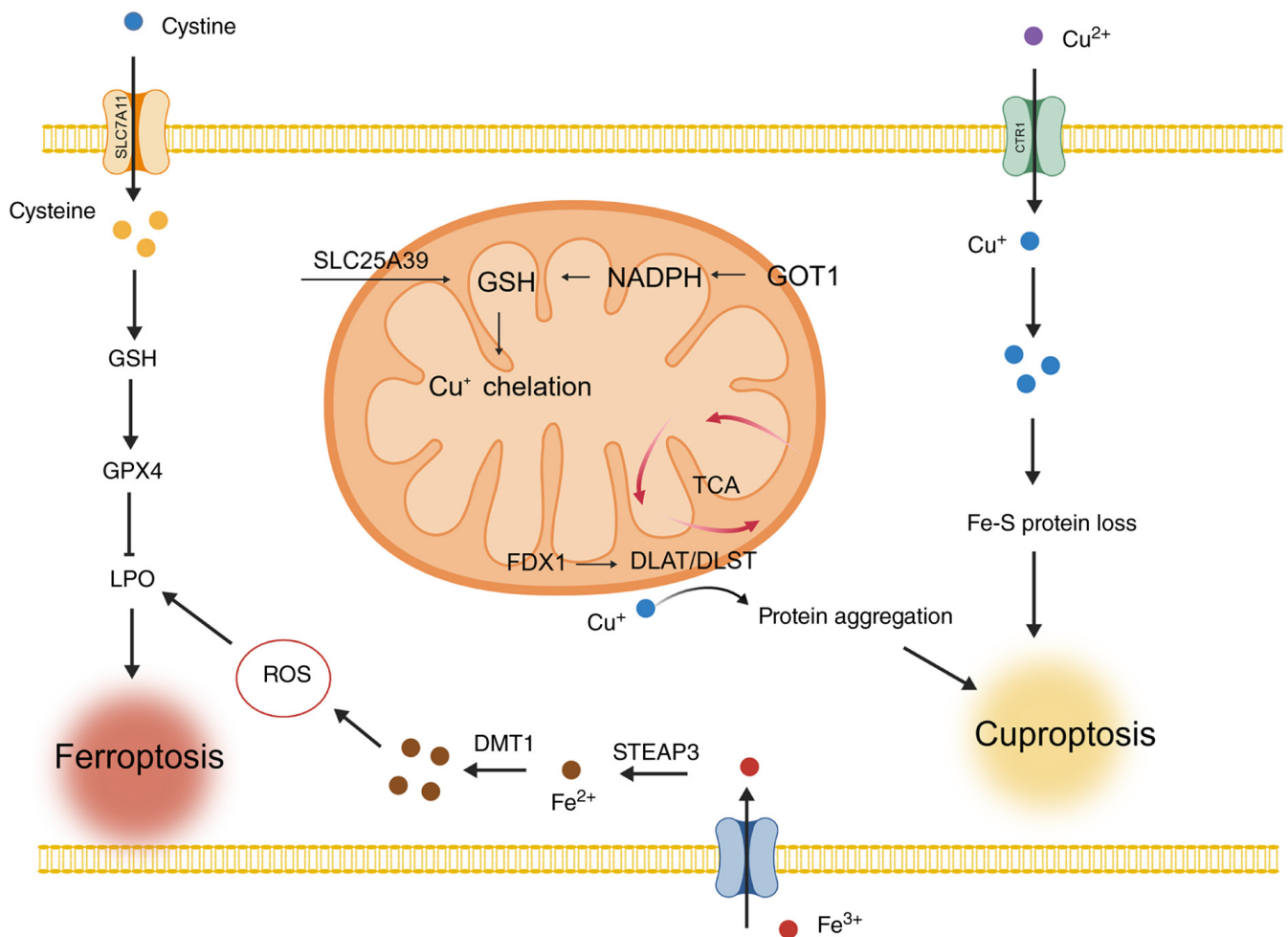


Figure 1. Core molecular pathways and interactive regulation of ferroptosis and cuproptosis in pancreatic ductal adenocarcinoma. The cystine-GSH-GPX4 axis regulates lipid peroxidation to induce ferroptosis. Copper ions cause mitochondrial damage and iron-sulfur cluster protein loss, thereby triggering cuproptosis. Key molecules related to iron metabolism and mitochondria participate in the cross-regulation of these two programmed cell death patterns. SLC7A11, solute carrier family 7 member 11; GSH, glutathione; GPX4, glutathione peroxidase 4; LPO, lipid peroxidation; ROS, reactive oxygen species; DMT1, divalent metal transporter 1; STEAP3, six transmembrane epithelial antigen of prostate 3; TCA, tricarboxylic acid; FDX1, ferredoxin 1; DLAT, dihydrolipoamide S-succinyltransferase; DLST, dihydrolipoamide S-succinyltransferase; Fe-S protein, iron-sulfur protein; CTR1, copper transporter 1.

protein lipoylation levels are elevated. Of note, such preferential susceptibility does not represent an absolute binary rule; the ultimate cell-death outcome is coordinately governed by multiple interacting metabolic determinants including iron-copper homeostasis GSH metabolism (11,31).

Impact of the TCA cycle on both cell death programs. The TCA cycle is located in the mitochondrial matrix and consists of a series of enzymatic reactions that form the central hub of aerobic metabolism. The TCA cycle is not only the final common pathway for the oxidative catabolism of carbohydrates, lipids and amino acids, but also a major source of biosynthetic precursors and reducing equivalents such as NADH (32). In tumour cells, the functional state of the TCA cycle directly influences proliferative capacity, adaptation to microenvironmental stress and responsiveness to various therapies. In PDAC, regulation of the TCA cycle displays a distinctive degree of complexity. KRAS mutations drive substantial glucose flux into the TCA cycle and concurrently enhance NADPH production through the pentose phosphate pathway, rendering tumour cells highly dependent on aerobic

glycolysis, whereby glucose is converted to lactate, as well as on glutamine anaplerosis (33). Son *et al* (34) further demonstrated that KRAS-mutant pancreatic cancer cells harbour an alternative glutamine metabolic bypass, which is distinct from the glutamate dehydrogenase 1-dependent pathway utilized by most tumours. PDAC cells use glutamine to generate aspartate through transamination reactions, and this aspartate can both enter the TCA cycle and support *de novo* nucleotide and amino acid synthesis. These characteristics place the TCA cycle at the centre of the metabolic network in PDAC.

The central mechanism of cuproptosis lies in the direct toxic effects of copper ions on specific mitochondrial proteins, which are key components of the TCA cycle. DLAT and DLST are the core catalytic subunits of the pyruvate dehydrogenase complex and the oxoglutarate dehydrogenase complex, respectively. The former catalyzes the conversion of pyruvate to acetyl-CoA, thereby linking glycolysis to the TCA cycle, whereas the latter catalyzes the conversion of α -ketoglutarate to succinyl-CoA and serves as a rate-limiting step in the TCA cycle (32). Tsvetkov *et al* (7) clearly demonstrated, using immunoblotting and native gel electrophoresis, that copper

treatment induces the formation of insoluble high-molecular-weight DLAT aggregates. In PDAC models, Yu *et al* (23) validated the applicability of this mechanism by showing that Elesclomol (ES)-Cu treatment induces marked accumulation of lipoylated DLAT in PDAC cell lines and primary tumour cells, and that this accumulation positively correlates with the extent of cell death. More importantly, PDAC cancer stem cells exhibit greater dependence on OXPHOS and higher TCA cycle activity, leading to elevated levels of lipoylated proteins and consequently increased sensitivity to cuproptosis (23). This finding suggests that the degree of TCA cycle activity may serve as a biomarker for predicting cuproptosis sensitivity in PDAC cells.

As a mitochondrial ferredoxin, FDX1 transfers reducing equivalents derived from FDX, preserves the functional integrity of cellular iron-sulfur cluster-containing enzymes and sustains core mitochondrial metabolic homeostasis (35). FDX1 supplies reducing equivalents to maintain LIAS activity. The biosynthesis of lipoylation modifications relies on LIAS, whereas Cu⁺ directly interferes with the mitochondrial TCA cycle. Nevertheless, given the importance of mitochondrial metabolism and the TCA cycle in PDAC, the FDX1-LIAS-lipoylation axis is likely to play an important role in the regulation of metal-dependent cell death in this disease.

Although the TCA cycle is not a direct executor of ferroptosis, it can profoundly influence ferroptosis sensitivity by regulating the supply of reducing equivalents. NADPH is a key cofactor for maintaining the cellular reducing environment, with major functions including supporting GSH regeneration through GSH reductase, supporting the mitochondrial GSH antioxidant system in scavenging ROS, and participating in biosynthetic reactions such as fatty acid synthesis (36). In the context of ferroptosis, an adequate supply of NADPH is essential for maintaining GSH levels and GPX4 activity. The TCA cycle can influence NADPH production through two major routes. The first is a direct route: Mitochondrial NADP⁺-dependent isocitrate dehydrogenase 2 catalyses the oxidative decarboxylation of isocitrate to α -ketoglutarate while reducing NADP⁺ to NADPH (36). The second is an indirect route: Citrate generated by the TCA cycle can be exported to the cytosol through the mitochondrial citrate transporter SLC25A1 (37). Citrate generated by the mitochondrial TCA cycle is shuttled to the cytosol via SLC25A1, where it is catalyzed by ATP-citrate lyase to produce acetyl-CoA and oxaloacetate. Oxaloacetate is subsequently reduced to malate by malate dehydrogenase, and cytosolic malic enzyme mediates the oxidative decarboxylation of malate to pyruvate, coupled with NADPH generation. In proliferative tumors such as glioblastoma, this pathway serves as a critical reductive source of reducing power independent of the pentose phosphate pathway (38). In PDAC, Kremer *et al* (11) directly elucidated this link. Inhibition of GOT1 disrupts the malate-aspartate shuttle, leading to reduced cytosolic NADPH production, decreased GSH levels and impaired GPX4 activity, thereby markedly increasing the sensitivity of PDAC cells to ferroptosis inducers. This finding reveals an intrinsic link between TCA cycle-associated metabolite shuttling and ferroptosis sensitivity, suggesting that targeting TCA cycle metabolism may represent a therapeutic strategy for sensitising PDAC to ferroptosis.

Involvement of Fe-S clusters in the interaction between death pathways. Fe-S clusters provide a deeper level of mechanistic interconnection. In PDAC and other malignancies, the integrity of the Fe-S cluster biosynthetic machinery is essential for maintaining mitochondrial function and cell survival. Alvarez *et al* (39) found that cysteine desulfurase 1, the rate-limiting enzyme for Fe-S cluster biogenesis, undergoes genomic amplification and is upregulated in multiple tumours, including lung adenocarcinoma. By maintaining intracellular Fe-S cluster homeostasis, this protein mitigates hyperoxia-triggered oxidative damage, restrains excessive accumulation of labile iron and thereby protects tumor cells from ferroptosis (39). This finding suggests that Fe-S cluster biogenesis is not only a fundamental metabolic process but also an important defence mechanism by which tumour cells cope with metal-dependent cell death stress. Loss of Fe-S cluster proteins is one of the hallmarks of cuproptosis, and in PDAC cancer stem cell models, ES-Cu treatment is likewise accompanied by a reduction in Fe-S cluster proteins (23). Although direct evidence is still lacking to show how loss of Fe-S clusters alters ferroptosis sensitivity in PDAC, mechanistically, such disruption would be expected to reshape mitochondrial metabolism, iron utilization and redox balance, thereby altering the threshold for ferroptosis. This level of interaction is mechanistically plausible in PDAC, but the causal chain remains to be further validated (7). The potential link between Fe-S clusters and ferroptosis is first reflected at the level of iron metabolism. The mitochondrial and cytosolic Fe-S cluster assembly pathways continuously utilise labile ferrous iron for the biosynthesis of metal cofactors. Functional impairment of these pathways leads to a marked elevation in cellular labile iron levels (40). Upon impairment of Fe-S cluster biogenesis, iron-regulatory protein 1 (IRP1) loses its [4Fe-4S] Fe-S cofactor and switches to an RNA-binding conformation, accompanied by mitochondrial iron accumulation. Activated IRPs bind to iron-responsive elements on iron-metabolism-related mRNAs, repress ferritin translation and stabilize transferrin receptor mRNA. Collectively, these events collectively increase cellular iron uptake and diminish iron storage (40,41).

This mechanism suggests that the loss of Fe-S proteins during cuproptosis may indirectly alter cellular iron homeostasis and affect ferroptosis sensitivity by perturbing IRP1 function. Although this hypothesis has not yet been directly validated experimentally in PDAC, existing studies have shown that defects in Fe-S cluster synthesis can markedly sensitise various cell types to ferroptosis inducers (39). These findings imply that the Fe-S cluster-IRP1-iron metabolism axis may represent an important molecular pathway linking cuproptosis and ferroptosis.

GPX4 links cuproptosis and ferroptosis. Ferroptosis and cuproptosis do not merely share upstream regulators such as GSH and mitochondria. Research has shown that copper itself can directly promote ferroptosis. GPX4 has been established as the enzyme that directly scavenges membrane lipid peroxides, and is therefore regarded as the master regulator of ferroptosis (42). In pancreatic cancer models, copper can bind to specific cysteine residues in GPX4, induce GPX4 aggregation and promote its degradation through a Tax1-binding

protein 1 (TAX1BP1)-mediated autophagic pathway, thereby amplifying ferroptotic effects; copper chelators, in contrast, attenuate this process. This finding directly links copper burden to GPX4, the key effector of ferroptosis (43).

In PDAC, GPX4 expression and activity directly determine tumour sensitivity to ferroptosis inducers. Zhu *et al* (12) found that HSPA5/GRP78 suppresses ferroptosis by stabilizing the GPX4 protein and mediates gemcitabine resistance in pancreatic cancer cells. GPX4 is therefore not merely a passive target in ferroptosis, but also an active molecular mediator of the crosstalk between copper- and iron-dependent cell death. Research has demonstrated that copper ions can directly bind to cysteine residues on the surface of GPX4, triggering conformational changes and oligomerization, followed by selective autophagic degradation mediated by the autophagy receptor TAX1BP1 (44). This mechanism reveals that copper can not only induce cuproptosis through mitochondrial lipoylated proteins, but can also directly amplify ferroptosis by promoting GPX4 degradation. Thus, the crosstalk between copper- and iron-dependent cell death extends from shared upstream metabolic nodes to direct molecular interactions. This suggests that copper-loading strategies in PDAC therapy should not be viewed merely as approaches to induce cuproptosis, but rather as dual-mode sensitisation strategies for metal-dependent cell death: They may predominantly induce cuproptosis in cells with active mitochondrial TCA cycling, while enhancing ferroptosis through GPX4 degradation in cells with high GPX4 expression but relatively suppressed mitochondrial metabolism.

Research has shown that mitochondrial GSH import does not occur through passive diffusion, but depends on the inner mitochondrial membrane transporter SLC25A39 (21). In PDAC, loss of SLC25A39 reduces mitochondrial GSH levels, but this alteration has distinctly different consequences for ferroptosis and cuproptosis. In ferroptosis, reduced mitochondrial GSH mainly affects GPX4 activity indirectly by decreasing the total intracellular GSH pool; in cuproptosis, however, the major role of mitochondrial GSH is to directly chelate or buffer Cu^+ in the mitochondrial matrix, thereby reducing the toxicity of copper towards lipoylated proteins. Therefore, the SLC25A39-mitochondrial GSH axis represents a key mitochondrial-level node of interaction between ferroptosis and cuproptosis.

In summary, ferroptosis and cuproptosis in PDAC are not independent cell-death modalities, but form a tightly regulated interactive network through multiple key nodes. GSH, mitochondrial metabolism, the TCA cycle, Fe-S cluster homeostasis and GPX4 collectively serve as core hubs linking these two death programmes. Nevertheless, this field still has notable limitations. Current investigations of the underlying interactive mechanisms are largely restricted to the verification of individual molecules or single pathways, whereas the broader synergistic and compensatory relationships among these hub pathways remain poorly defined, and a systematic interpretation of the integrated regulatory network is still lacking. Most mechanistic conclusions are derived from basic cellular experiments and have not been validated in consideration of PDAC heterogeneity, tumour microenvironment characteristics or metabolic differences among distinct

cellular subpopulations. Furthermore, direct experimental evidence confirming the causal regulatory relationships of critical axes, including the FDX1-LIAS lipoylation axis and the Fe-S cluster-IRP1 pathway, in PDAC remains insufficient.

4. Manifestations of ferroptosis-cuproptosis crosstalk in the PDAC tumor microenvironment

KRAS-driven metal-dependent cell death. KRAS mutation is a core driver event in PDAC, with >90% of cases harbouring recurrent functional mutations in exon 2, predominantly G12D, G12V and G12R (45). Beyond activating the RAF-MEK-ERK and PI3K-AKT signaling cascades to drive PDAC-cell proliferation and survival, mutant KRAS also rewires the global metabolic networks governing glucose, glutamine and lipid metabolism. PDAC cells under such regulation exhibit markedly elevated metabolic flux, intracellular ROS accumulation and enhanced nutrient-scavenging capacity within the tumour microenvironment (33,34). These adaptive alterations resulting from metabolic reprogramming render tumor cells heavily dependent on the GSH-GPX4 antioxidant system, as well as mitochondrial metabolism, to sustain homeostasis; this dependency in turn exposes therapeutically exploitable vulnerabilities within the regulatory pathways of ferroptosis and cuproptosis in PDAC.

KRAS-mediated metabolic reprogramming directly influences ferroptosis sensitivity in PDAC. Mutant KRAS markedly elevates intracellular ROS and lipid peroxide levels by activating the NADPH oxidase family and augmenting mitochondrial metabolic activity. Such oxidative stress compels tumour cells to rely on GPX4 for redox homeostasis, rendering KRAS-mutant cells profoundly sensitive to GPX4 inhibitors. This oxidative dependency also creates a therapeutically exploitable vulnerability of PDAC to the mitochondria-dependent cuproptosis pathway (46,47). In PDAC, KRAS activates NRF2- and activating transcription factor 4-dependent transcriptional programmes to upregulate antioxidant genes such as SLC7A11 and GCLC/GCLM, thereby compensating for high ROS stress and sustaining tumor survival (9). This compensatory pathway also creates a dependence on cystine metabolism; once cystine uptake is blocked or GPX4 is inhibited, the antioxidant system rapidly collapses, enabling KRAS-mutant PDAC cells to readily undergo ferroptosis (9).

KRAS further regulates cuproptosis sensitivity by reshaping mitochondrial metabolism. Conditional ablation of KRAS can shift PDAC metabolism from glycolysis toward OXPHOS, thereby enhancing mitochondrial respiration and TCA cycle activity (45). Based on the core mechanism of cuproptosis, increased OXPHOS would be expected to intensify copper-dependent stress responses in cells. PDAC cancer stem cells are highly dependent on mitochondrial OXPHOS for survival. The combination of ES and copper ions specifically triggers aggregation of the mitochondrially lipoylated DLAT protein, disrupts the homeostasis of Fe-S cluster-containing proteins and preferentially eliminates drug-resistant tumour cells with stem-like properties (48). Collectively, tumour heterogeneity arising from KRAS-driven metabolic divergence dictates differential responsiveness to regulated cell-death pathways among distinct cellular subsets:

Cells with high glycolytic propensity are prone to ferroptosis, whereas stem-like cells reliant on mitochondrial OXPHOS are more susceptible to elimination via cuproptosis.

In addition, KRAS may directly influence copper homeostasis and rewire metal-dependent programmed cell-death pathways, including ferroptosis and cuproptosis. BRAF-driven tumours express high levels of the copper transporter CTR1 and display pronounced copper-dependent proliferative behaviour; accordingly, copper chelators can reduce MEK phosphorylation, disrupt intratumoral copper ion homeostasis and effectively suppress KRAS-mediated tumour proliferation (49). Relevant mechanistic studies have verified that the copper transporter CTR1 mediates intracellular copper uptake and copper accumulation activates the MEK signaling pathway. Activated MEK further upregulates DNA methyltransferase 1, which epigenetically silences the tumour-suppressive microRNA (miR)-124 via methylation. This event relieves the transcriptional repression of CTR1 imposed by miR-124, thereby establishing a positive-feedback loop linking copper metabolism to tumour progression (50). This pathway reveals the dual copper dependency of PDAC: Copper serves as an essential cofactor sustaining KRAS-driven downstream proliferative signaling, whereas excessive copper accumulation initiates cuproptosis. Accordingly, differential intervention strategies can be considered, either suppressing tumour proliferation via copper depletion, or artificially inducing copper overload to trigger cuproptosis in tumour cells.

Finally, KRAS indirectly modulates the efficacy of metal-dependent cell death by remodelling the tumour microenvironment. In KRAS-driven PDAC models, although a high-iron diet or GPX4 deficiency can induce tumor ferroptosis, these interventions also release oxidative damage-associated molecules such as 8-hydroxy-2'-deoxyguanosine, aberrantly activate the stimulator of IFN response cGAMP interactor (STING) pathway, recruit inflammatory macrophages into the microenvironment and ultimately accelerate tumour progression. This tumour-promoting effect can be completely reversed by ferroptosis inhibitors, macrophage depletion or STING pathway blockade (8). These findings indicate that in KRAS-mutant PDAC, ferroptosis is not uniformly tumour suppressive; rather, its ultimate effect depends on timing, intensity and microenvironmental context, and may lead either to immune-mediated tumor clearance or to inflammation-driven tumour promotion.

Badgley *et al* (9) demonstrated in a Kras/Trp53-driven mouse model of PDAC that depletion of exogenous cysteine or cystine induces tumour-selective necrosis-like degeneration accompanied by marked lipid peroxidation and features consistent with ferroptosis. This finding indicates that these tumours are highly dependent on cysteine metabolism and on defences against lipid peroxidation, and it remains one of the most compelling *in vivo* demonstrations of ferroptosis in PDAC. Wang *et al* (51) further showed, in the context of cancer immunotherapy, that CD8⁺ T-cells promote ferroptosis by using IFN- γ to suppress cystine uptake by tumour cells, thereby enhancing antitumour activity. Together, these studies support the view that ferroptosis induction has tumour-suppressive potential. However, ferroptosis is not invariably a purely antitumour process. Friedmann Angeli *et al* (42) showed that GPX4 loss-induced ferroptosis can cause substantial tissue

injury, while Tang *et al* (52) emphasised that lipid peroxidation products, damage-associated molecular patterns and secondary inflammatory responses generated during ferroptosis may have markedly different consequences depending on the microenvironment. This issue is particularly relevant in PDAC, whose microenvironment is rich in fibroblasts, macrophages, and inflammatory mediators. In this setting, Dai *et al* (53) reported that autophagy-dependent ferroptosis can drive tumour-associated macrophage polarisation through the release and uptake of oncogenic KRAS protein, thereby exerting potentially pro-tumour effects. Ferroptosis in PDAC should therefore be regarded as a double-edged sword: It may act as a mechanism of tumour cell killing, but it may also promote a tumour-supportive microenvironment through oxidised lipids, inflammatory signalling and immune remodelling.

A similar conceptual tension exists in relation to cuproptosis. Besides the view that copper overload suppresses tumours by inducing cuproptosis, another line of evidence suggests that copper depletion may also inhibit tumour growth. Early clinical studies showed that decoupling strategies, such as treatment with tetrathiomolybdate, can suppress tumour progression through anti-angiogenic effects (54). Copper is also an essential cofactor in Ras/MAPK signaling, meaning that restriction of copper availability may itself attenuate oncogenic signal output (55). These observations suggest that copper overload-induced cuproptosis and copper chelation-mediated tumour suppression are not necessarily contradictory, but instead reflect the dual nature of copper in cancer biology. Tumour growth requires a basal supply of copper, whereas copper levels beyond a tolerable threshold may become cytotoxic and trigger cuproptosis. Accordingly, even when cuproptosis-related genes such as FDX1, LIAS, LIPT1 and DLAT are associated with patient prognosis or immune infiltration in public datasets, such findings should be interpreted as correlative rather than mechanistic. They do not demonstrate that cuproptosis is genuinely occurring in patients *in vivo* (56).

CAFs regulate the balance between ferroptosis and cuproptosis. PDAC is characterised by a desmoplastic stromal microenvironment, with CAFs constituting the predominant cellular population within the stroma (57). Studies have revealed marked functional heterogeneity among CAFs, which can be subdivided into myofibroblastic CAFs, inflammatory CAFs (iCAFs) and antigen-presenting CAFs, among other subpopulations (58,59). Different CAF subtypes exhibit substantial differences in their regulation of metal ion homeostasis in tumour cells. However, they collectively modulate both cuproptosis and ferroptosis in tumour cells (Fig. 2).

From the perspective of iron metabolism, CAFs remodel iron homeostasis in tumor cells through the secretion of multiple cytokines. Studies in a variety of tumour cells, including pancreatic cancer cells, have shown that iCAFs express high levels of interleukin-6, which upregulates ferritin expression in tumour cells through the STAT3 signaling pathway, thereby sequestering labile iron and reducing ferroptosis sensitivity (60,61). In addition, CAF-derived exosomes carrying miR-522 can suppress ALOX15 expression, thereby blocking lipid peroxidation. This confers ferroptosis resistance

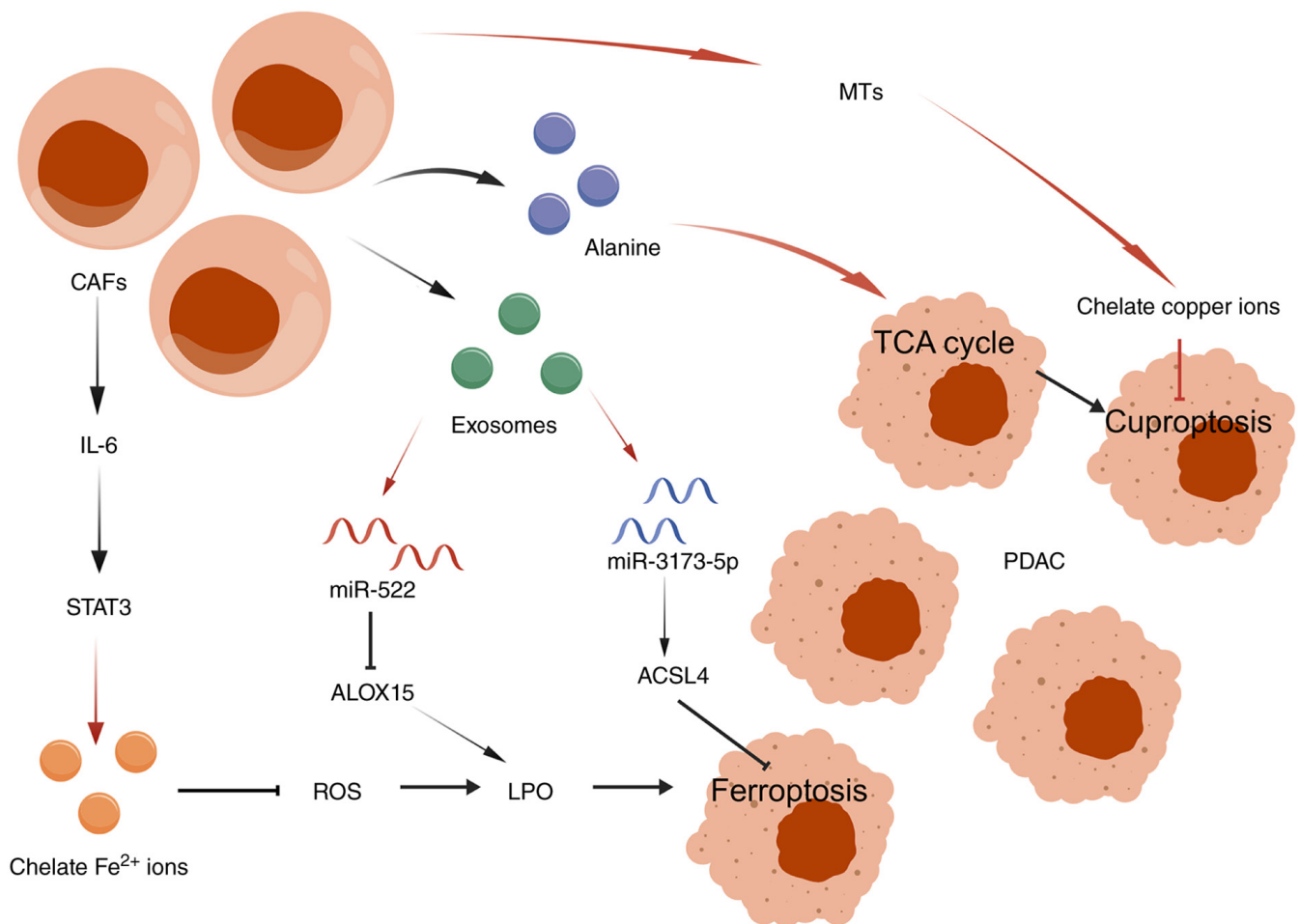


Figure 2. Schematic diagram of CAFs regulating the balance between ferroptosis and cuproptosis CAFs modulate key ferroptosis molecules ALOX15 and ACSL4 via the IL-6/STAT3 axis, exosomal miRNAs and metabolite secretion. They also mediate copper metabolism through alanine and MTs, thus regulating the homeostasis of ferroptosis and cuproptosis in PDAC cells (pathways and regulatory relationships that have been experimentally established are drawn with solid black lines, whereas hypothetical, inferred or indirect pathways are drawn with red lines). CAF, cancer-associated fibroblast; IL-6, interleukin-6; STAT3, signal transducer and activator of transcription 3; ROS, reactive oxygen species; TCA, tricarboxylic acid; miRNA, microRNA; PDAC, pancreatic ductal adenocarcinoma; MTs, metallothioneins; ALOX15, arachidonate 15-lipoxygenase; ACSL4, acyl-CoA synthetase long chain family member 4; LPO, lipid peroxidation.

on tumour cells, a conclusion that has been validated in gastric cancer models (62).

At the level of copper metabolism, the role of CAFs is likewise non-negligible. Studies have shown that activated fibroblasts secrete metallothioneins, proteins with strong copper-binding capacity that can reduce the concentration of free copper ions in the microenvironment (63,64). More importantly, CAFs highly express the copper transporters ATPase copper transporting α (ATP7A) and ATP7B, enabling active uptake and efflux of copper ions, a process that may influence the sensitivity of neighboring tumour cells to cuproptosis, a conclusion that has been verified in a variety of gastrointestinal tumor cells (65).

CAF and tumor cells are tightly metabolically coupled and this relationship plays a central role in the interactive regulation of cuproptosis and ferroptosis. Studies have shown that pancreatic stellate cells (PSCs) constitute the principal cellular origin of CAFs in pancreatic cancer, and that PSCs secrete alanine for utilization by tumour cells (66). This metabolite transfer can directly influence TCA cycle activity in tumour cells. Given that cuproptosis depends on active TCA cycling

and the abundance of lipoylated proteins (7), CAF-mediated metabolic support may increase tumour cell sensitivity to cuproptosis.

At the same time, cysteine secreted by CAFs serves as an important precursor for GSH synthesis in tumour cells (67). As a key suppressor of ferroptosis, GSH enables GPX4-mediated detoxification of lipid peroxides (4). Therefore, CAFs enhance tumour cell resistance to ferroptosis by supplying cysteine. Because GSH also participates in copper chelation and detoxification, CAF-derived cysteine may simultaneously regulate both cuproptotic and ferroptotic pathways (67).

CAF can also mediate tumour drug resistance through exosomal signalling. Available evidence indicates that CAF-derived exosomal miR-3173-5p targets ACSL4, suppresses ferroptosis and induces gemcitabine resistance in PDAC cells. ACSL4 directly participates in the remodelling membrane lipid composition and is a key functional molecule in promoting lipid peroxidation and initiating ferroptosis. These findings indicate that CAFs do not merely provide nutritional support, but can also directly reprogram the lipid susceptibility of tumor cells (68).

Effects of hypoxia on the two cell death programs. Pancreatic cancer is characterised by severe tissue hypoxia, with intratumoural oxygen tension reported to be as low as 0–5 mmHg (69). Hypoxia-inducible factors (HIFs), the master regulators of the hypoxic response, profoundly influence both iron and copper metabolic networks.

In iron metabolism, HIF-1 α and HIF-2 α influence cellular iron homeostasis through the transcriptional regulation of multiple key genes. HIF-2 α directly activates the expression of divalent metal transporter 1 to enhance intestinal dietary iron uptake, whereas HIF-1 α transcriptionally upregulates transferrin receptor to mediate cellular uptake of transferrin-bound iron (70). In the liver, research has shown that HIF-1 α mediates the transcriptional downregulation of hepcidin, which relieves inhibition of ferroportin and indirectly augments intestinal iron absorption and macrophage iron release (71). However, changes in ferroptosis sensitivity under hypoxic conditions are complex. Although iron accumulation would theoretically increase vulnerability to ferroptosis, hypoxia can markedly suppress oxygen-dependent lipid peroxidation.

At the level of copper metabolism, hypoxia also exerts important regulatory effects. Research in lung-related systems indicate that hypoxia induces marked accumulation of HIF-1 α , which concurrently activates copper-transport-related genes such as CTR and ATP7A (72). In addition, under hypoxic conditions, mitochondrial electron transport chain activity is impaired and TCA cycle dependence is reduced, which may weaken the execution of cuproptosis. Research in tumour cells including pancreatic cancer cells further reveal that hypoxia induces upregulation of the lysyl oxidase (LOX) family proteins, thereby promoting extracellular matrix cross-linking and tumour metastasis. These findings suggest that, under hypoxic conditions, the biological role of copper may shift from inducing cell death to facilitating tumour progression (73).

The pancreatic cancer microenvironment is characterised by cyclic fluctuations between hypoxia and reoxygenation, and this dynamic variation may be highly relevant to the transition between cuproptosis and ferroptosis (74). During reoxygenation, ROS are generated in bursts, which can promote iron-dependent lipid peroxidation through the Fenton reaction and enhance ferroptosis, while simultaneously causing oxidative damage to mitochondrial lipoylated proteins and thereby affecting the course of cuproptosis.

Recent research in PDAC has found that pancreatic tumour interstitial fluid acts synergistically with hypoxia to markedly enhance resistance to ferroptosis through HIF-2-mediated mechanisms (75). When considered alongside studies of epithelial-mesenchymal transition (EMT) heterogeneity, these findings suggest that the PDAC microenvironment does not uniformly suppress ferroptosis; rather, through the combined effects of hypoxia, nutrient composition and cellular state, it establishes a layered protective landscape in which mesenchymal-like cells depend more heavily on cysteine, whereas epithelial-like cells rely more on thioredoxin-based defenses.

Interactive regulation of EMT, ferroptosis and cuproptosis. EMT is a core program driving invasion and metastasis in pancreatic cancer. Recent research has revealed a close association between EMT status and ferroptosis sensitivity. Research has demonstrated that tumour cells with

a mesenchymal phenotype are highly sensitive to GPX4 inhibitor-induced ferroptosis. The core EMT transcription factor zinc finger E-box binding homeobox 1 modulates the expression of fatty-acid synthases-related enzymes, including ACSL4 and fatty acid desaturase 2, elevates the proportion of pro-oxidative polyunsaturated phospholipids in cell membranes and renders tumor cells highly susceptible to GPX4-inhibitor-triggered ferroptosis (76). Drug-tolerant persister cells are accompanied by EMT and global repression of the Nrf2-mediated antioxidant pathway. Insufficient reserves of GSH and NADPH impair the capacity to eliminate lipid peroxides, rendering these cells highly vulnerable to ferroptosis upon GPX4 inhibition. This phenomenon has been validated in multiple tumour cell types, including lung cancer cells (77). Compared with the extensively studied relationship between ferroptosis and EMT, the link between copper metabolism and EMT has only recently begun to attract attention. As a cofactor for multiple redox enzymes, copper participates in EMT-related extracellular matrix remodeling. LOX and LOX-like 2 are both copper-dependent enzymes that play key roles in catalysing the cross-linking of collagen and elastin; this has been validated in tumour cells, including pancreatic cancer cells (73,78).

Research has shown that elevated intracellular copper levels in PDAC cells can activate copper-dependent transcription factors and thereby upregulate core EMT transcription factors (79). This finding suggests that, while copper ions promote EMT, they may simultaneously render cells more susceptible to cuproptotic attack by enhancing TCA cycle activity, thereby creating a self-limiting feedback mechanism.

Bidirectional regulation by the immune microenvironment. The immune microenvironment of PDAC is highly immunosuppressive, as reflected by increased infiltration of regulatory T cells, impaired function of cytotoxic T lymphocytes and enrichment of M2-polarized tumour-associated macrophages (TAMs) (80). Whether cuproptosis and ferroptosis are immunogenic, that is, whether they can induce immunogenic cell death, has become a major focus of current research.

The immunogenic features of ferroptosis have been preliminarily demonstrated. Studies in pancreatic cancer cells indicate that damage-associated molecular patterns released from ferroptotic cells, including high mobility group box 1 (HMGB1), ATP and calreticulin exposure, can effectively promote dendritic cell maturation and T-cell priming (52,81). In addition, oxidised phospholipids generated during ferroptosis serve to facilitate the recognition and clearance of ferroptotic cells by phagocytes. This process has been validated in haematological malignancies (82).

By contrast, research into the immunogenicity of cuproptosis remains at an early stage. Preliminary evidence suggests that cuproptosis-induced mitochondrial protein aggregation may trigger the release of mitochondrial DNA, activate the cyclic GMP-AMP synthase-stimulator of IFN response cGAMP interactor signaling pathway and induce type I IFN production, thereby exerting potential immune-activating effects; this hypothesis has been validated in breast cancer cells (83).

Immune cells are not only effectors of cuproptosis and ferroptosis, but are themselves also regulated by these two

cell death programs. Macrophages, as major innate immune cells in the tumour microenvironment, exhibit polarization states that are closely linked to iron metabolism. M1 macrophages express high levels of ferritin and thus possess strong iron-storage capacity and resistance to ferroptosis, whereas M2 macrophages express high levels of membrane iron transport proteins and tend to release iron into the microenvironment (84). This difference makes induction of ferroptosis in M2-type TAMs a potential strategy for remodelling the tumour immune microenvironment.

The effector function of CD8⁺ T cells is likewise regulated by ferroptosis. Research has shown that activated CD8⁺ T cells can downregulate SLC7A11 expression in tumor cells through the secretion of IFN- γ , thereby promoting tumour cell ferroptosis (51). This finding highlights the important role of ferroptosis in immune surveillance. However, sustained ferroptotic signaling may also contribute to T-cell exhaustion. Research has demonstrated that lipid peroxides within the tumour microenvironment can induce ferroptosis in CD8⁺ T cells, thereby weakening antitumor immune responses (85).

Based on these findings, combining the induction of cuproptosis or ferroptosis with immune checkpoint blockade may represent a new strategy for overcoming immunotherapy resistance in PDAC. Combination of ferroptosis inducers with anti-programmed cell death-1/programmed cell death ligand 1 (PD-L1) antibodies can markedly enhance antitumor immune responses. The underlying mechanism involves HMGB1 release-driven dendritic cell activation and enhanced cross-presentation of tumour antigens. Nevertheless, this effect exhibits phase-dependent properties; lipid peroxides generated in late-stage ferroptosis conversely impair the antigen-presenting function of dendritic cells (86).

With respect to cuproptosis, the copper ionophore ES has shown synergistic potential when combined with immunotherapy. ES-induced cuproptosis can enhance the antigen-presenting capacity of tumour cells and upregulate major histocompatibility complex class I expression, thereby increasing sensitivity to combination therapy (31). In addition, nanodrug delivery systems provide a technological platform for the precise induction of cuproptosis and ferroptosis, as well as for remodeling the immune microenvironment (87).

Resistance to ferroptosis is closely associated with chemoresistance in PDAC. Mechanisms such as the HSPA5-GPX4 axis have been shown to block gemcitabine-induced ferroptosis and promote PDAC chemoresistance (12).

From the perspective of cuproptosis, CSCs with more active OXPHOS and greater stemness may represent a promising therapeutic vulnerability. ES-Cu combined with copper nanoparticles can preferentially target the CSC phenotype and improve the efficacy of gemcitabine in immunocompetent mice. In parallel, a Pt@PCN-Cu nanosystem (a cascade nanozyme with platinum nanoparticles encapsulated in copper-modified porous coordination network metal-organic framework for synergistic cuproptosis-immunotherapy of pancreatic cancer) has been developed to induce cuproptosis in PDAC and upregulate PD-L1 through a hexokinase 2-related mechanism; when combined with anti-PD-L1 therapy, this system yields stronger tumour suppression and more

pronounced microenvironmental remodelling (88). Recent research has further indicated that CTR1-driven copper metabolism can promote neutrophil infiltration, suggesting that copper homeostasis itself is an important determinant of the immunosuppressive microenvironment (19).

5. Conclusions and perspectives

In summary, ferroptosis and cuproptosis in PDAC are not two parallel, independent pathways; rather, they constitute an integrated cell death regulatory system that shares GSH, mitochondrial function and stress-responsive transcriptional networks. The NFE2L2-GSH-SLC25A39 axis simultaneously influences resistance to both cuproptosis and ferroptosis; mitochondrial TCA cycle activity, lipoylation status and Fe-S cluster integrity determine cuproptosis sensitivity while also reshaping the threshold of ferroptosis; furthermore, copper can directly amplify ferroptosis through autophagic degradation of GPX4.

Notably, this field still exhibits substantial asymmetry in the depth of available evidence. Mechanistic studies of ferroptosis in PDAC are relatively mature, whereas investigations of cuproptosis supported by functional and *in vivo* validation remain limited. At present, the most robust evidence for cuproptosis in PDAC is concentrated in a few areas, including the NFE2L2/SLC25A39/GSH mechanism, CSC-targeted cuproptosis and nanomaterial-assisted combination immunotherapy, whereas a large proportion of studies remain limited to transcriptomic scoring or prognostic modelling.

Future research should focus on at least four major directions. First, the conditions under which PDAC cells switch between cuproptosis and ferroptosis need to be clarified, particularly the dynamics of copper distribution between mitochondria and the cytosol. Second, spatial transcriptomics combined with metal imaging should be used to resolve the division of labour in iron, copper and GSH metabolism among tumor cells, CAFs and immune cells. Third, biomarker systems applicable to patient stratification should be established, including KRAS status, SLC31A1/CTR1, FDX1, lipoylated DLAT, SLC25A39, GPX4, EMT status and HIF-2 activity (89). Fourth, drug delivery systems tailored to the poorly perfused PDAC microenvironment should be developed to overcome the translational bottleneck whereby agents are effective *in vitro* but fail within the pancreatic stroma *in vivo*.

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Authors' contributions

WL was involved in conceptualization, investigation, literature search and writing the original draft. MD was responsible for conceptualization, investigation, literature curation and writing the original draft. RJ performed investigation and literature curation. ZQ was involved in investigation and literature curation. RL contributed to investigation and literature curation. PC was responsible for conceptualization, investigation, project administration, supervision, validation, visualization, and reviewing and editing. LL contributed to conceptualization, investigation, project administration, supervision, validation, visualization, and reviewing and editing. Data authentication is not applicable. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

References

- Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 74: 229-263, 2024.
- Park W, Chawla A and O'Reilly EM: Pancreatic cancer: A review. *JAMA* 326: 851-862, 2021.
- Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, *et al*: Ferroptosis: An iron-dependent form of nonapoptotic cell death. *Cell* 149: 1060-1072, 2012.
- Yang WS, SriRamaratnam R, Welsch ME, Shimada K, Skouta R, Viswanathan VS, Cheah JH, Clemons PA, Shamji AF, Clish CB, *et al*: Regulation of ferroptotic cancer cell death by GPX4. *Cell* 156: 317-331, 2014.
- Bersuker K, Hendricks JM, Li Z, Magtanong L, Ford B, Tang PH, Roberts MA, Tong B, Maimone TJ, Zoncu R, *et al*: The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. *Nature* 575: 688-692, 2019.
- Mao C, Liu X, Zhang Y, Lei G, Yan Y, Lee H, Koppula P, Wu S, Zhuang L, Fang B, *et al*: DHODH-mediated ferroptosis defence is a targetable vulnerability in cancer. *Nature* 593: 586-590, 2021.
- Tsvetkov P, Coy S, Petrova B, Dreishpoon M, Verma A, Abdusamad M, Rossen J, Joesch-Cohen L, Humeidi R, Spangler RD, *et al*: Copper induces cell death by targeting lipoylated TCA cycle proteins. *Science* 375: 1254-1261, 2022.
- Dai E, Han L, Liu J, Xie Y, Zeh HJ, Kang R, Bai L and Tang D: Ferroptotic damage promotes pancreatic tumorigenesis through a TMEM173/STING-dependent DNA sensor pathway. *Nat Commun* 11: 6339, 2020.
- Badgley MA, Kremer DM, Maurer HC, DelGiorno KE, Lee HJ, Purohit V, Sagalovskiy IR, Ma A, Kapilian J, Firl CEM, *et al*: Cysteine depletion induces pancreatic tumor ferroptosis in mice. *Science* 368: 85-89, 2020.
- Doll S, Proneth B, Tyurina YY, Panzilius E, Kobayashi S, Ingold I, Irmeler M, Beckers J, Aichler M, Walch A, *et al*: ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. *Nat Chem Biol* 13: 91-98, 2017.
- Kremer DM, Nelson BS, Lin L, Yarosz EL, Halbrook CJ, Kerk SA, Sajjakulnukit P, Myers A, Thurston G, Hou SW, *et al*: GOT1 inhibition promotes pancreatic cancer cell death by ferroptosis. *Nat Commun* 12: 4860, 2021.
- Zhu S, Zhang Q, Sun X, Zeh HJ, Lotze MT, Kang R and Tang D: HSPA5 regulates ferroptotic cell death in cancer cells. *Cancer Res* 77: 2064-2077, 2017.
- Luo Z, Zheng Q, Ye S, Li Y, Chen J, Fan C, Chen J, Lei Y, Liao Q and Xi Y: HMGA2 alleviates ferroptosis by promoting GPX4 expression in pancreatic cancer cells. *Cell Death Dis* 15: 220, 2024.
- Zhang W, Gong M, Zhang W, Mo J, Zhang S, Zhu Z, Wang X, Zhang B, Qian W, Wu Z, *et al*: Thiostrepton induces ferroptosis in pancreatic cancer cells through STAT3/GPX4 signalling. *Cell Death Dis* 13: 630, 2022.
- Kuang F, Liu J, Xie Y, Tang D and Kang R: MGST1 is a redox-sensitive repressor of ferroptosis in pancreatic cancer cells. *Cell Chem Biol* 28: 765-775.e5, 2021.
- Ohgami RS, Campagna DR, McDonald A and Fleming MD: The steap proteins are metalloredutases. *Blood* 108: 1388-1394, 2006.
- Nevitt T, Ohrvik H and Thiele DJ: Charting the travels of copper in eukaryotes from yeast to mammals. *Biochim Biophys Acta* 1823: 1580-1593, 2012.
- Kuo YM, Zhou B, Cosco D and Gitschier J: The copper transporter CTR1 provides an essential function in mammalian embryonic development. *Proc Natl Acad Sci USA* 98: 6836-6841, 2001.
- Lener MR, Scott RJ, Wiechowska-Kozłowska A, Serrano-Fernández P, Baszuk P, Jaworska-Bieniek K, Sukiennicki G, Marciniak W, Muszyńska M, Kładny J, *et al*: Serum concentrations of selenium and copper in patients diagnosed with pancreatic cancer. *Cancer Res Treat* 48: 1056-1064, 2016.
- Song G, Dong H, Ma D, Wang H, Ren X, Qu Y, Wu H, Zhu J, Song W, Meng Y, *et al*: Tetrahedral framework nucleic acid delivered RNA therapeutics significantly attenuate pancreatic cancer progression via inhibition of CTR1-dependent copper absorption. *ACS Appl Mater Interfaces* 13: 46334-46342, 2021.
- Wang Y, Yen FS, Zhu XG, Timson RC, Weber R, Xing C, Liu Y, Allwein B, Luo H, Yeh HW, *et al*: SLC25A39 is necessary for mitochondrial glutathione import in mammalian cells. *Nature* 599: 136-140, 2021.
- Liu J, Tang H, Chen F, Li C, Xie Y, Kang R and Tang D: NFE2L2 and SLC25A39 drive cuproptosis resistance through GSH metabolism. *Sci Rep* 14: 29579, 2024.
- Yu Q, Jiang K, Ma S, Zheng Q, Tondi S, Reina C, Šabanović B, Wen C, Shen B, Aicher A, *et al*: Elesclomol-copper combination synergistically targets mitochondrial metabolism in cancer stem cells to overcome chemoresistance in PDAC. *Mol Ther* 33: 6160-6177, 2025.
- Lushchak VI: Glutathione homeostasis and functions: Potential targets for medical interventions. *J Amino Acids* 2012: 1-26, 2012.
- Chen L, Ning J, Linghu L, Tang J, Liu N, Long Y, Sun J, Lv C, Shi Y, Tao T, *et al*: USP13 facilitates a ferroptosis-to-autophagy switch by activation of the NFE2L2/NRF2-SQSTM1/p62-KEAP1 axis dependent on the KRAS signaling pathway. *Autophagy* 21: 565-582, 2025.
- Wang S, Chao X, Jiang X, Wang T, Rodriguez Y, Yang L, Pacher P, Ni HM and Ding WX: Loss of acinar cell VMP1 triggers spontaneous pancreatitis in mice. *Autophagy* 18: 1572-1582, 2022.
- Gao M, Yi J, Zhu J, Minikes AM, Monian P, Thompson CB and Jiang X: Role of mitochondria in ferroptosis. *Mol Cell* 73: 354-363.e3, 2019.
- Tadokoro T, Ikeda M, Ide T, Deguchi H, Ikeda S, Okabe K, Ishikita A, Matsushima S, Koumura T, Yamada KI, *et al*: Mitochondria-dependent ferroptosis plays a pivotal role in doxorubicin cardiotoxicity. *JCI Insight* 5: e132747, 2020.
- Rowland EA, Snowden CK and Cristea IM: Protein lipoylation: An evolutionarily conserved metabolic regulator of health and disease. *Curr Opin Chem Biol* 42: 76-85, 2018.
- Cobine PA and Brady DC: Cuproptosis: Cellular and molecular mechanisms underlying copper-induced cell death. *Mol Cell* 82: 1786-1787, 2022.
- Ge EJ, Bush AI, Casini A, Cobine PA, Cross JR, DeNicola GM, Dou QP, Franz KJ, Gohil VM, Gupta S, *et al*: Connecting copper and cancer: From transition metal signalling to metalloplasia. *Nat Rev Cancer* 22: 102-113, 2022.

32. Martínez-Reyes I and Chandel NS: Mitochondrial TCA cycle metabolites control physiology and disease. *Nat Commun* 11: 102, 2020.
33. Ying H, Kimmelman AC, Lyssiotis CA, Hua S, Chu GC, Fletcher-Sanankione E, Locasale JW, Son J, Zhang H, Coloff JL, *et al*: Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. *Cell* 149: 656-670, 2012.
34. Son J, Lyssiotis CA, Ying H, Wang X, Hua S, Ligorio M, Perera RM, Ferrone CR, Mullarky E, Shyh-Chang N, *et al*: Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. *Nature* 496: 101-105, 2013.
35. Shi Y, Ghosh M, Kovtunovych G, Crooks DR and Rouault TA: Both human ferredoxins 1 and 2 and ferredoxin reductase are important for iron-sulfur cluster biogenesis. *Biochim Biophys Acta* 1823: 484-492, 2012.
36. Jiang L, Shestov AA, Swain P, Yang C, Parker SJ, Wang QA, Terada LS, Adams ND, McCabe MT, Pietrak B, *et al*: Reductive carboxylation supports redox homeostasis during anchorage-independent growth. *Nature* 532: 255-258, 2016.
37. Li Y, Li YC, Liu XT, Zhang L, Chen YH, Zhao Q, Gao W, Liu B, Yang H and Li P: Blockage of citrate export prevents TCA cycle fragmentation via Irg1 inactivation. *Cell Rep* 38: 110391, 2022.
38. DeBerardinis RJ, Mancuso A, Daikhin E, Nissim I, Yudkoff M, Wehrli S and Thompson CB: Beyond aerobic glycolysis: Transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. *Proc Natl Acad Sci USA* 104: 19345-19350, 2007.
39. Alvarez SW, Sviderskiy VO, Terzi EM, Papagiannakopoulos T, Moreira AL, Adams S, Sabatini DM, Birsoy K and Possemato R: NFS1 undergoes positive selection in lung tumours and protects cells from ferroptosis. *Nature* 551: 639-643, 2017.
40. Rouault TA: Biogenesis of iron-sulfur clusters in mammalian cells: New insights and relevance to human disease. *Dis Models Mech* 5: 155-164, 2012.
41. Anderson CP, Shen M, Eisenstein RS and Leibold EA: Mammalian iron metabolism and its control by iron regulatory proteins. *Biochim Biophys Acta* 1823: 1468-1483, 2012.
42. Friedmann Angeli JP, Schneider M, Proneth B, Tyurina YY, Tyurin VA, Hammond VJ, Herbach N, Aichler M, Walch A, Eggenhofer E, *et al*: Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. *Nat Cell Biol* 16: 1180-1191, 2014.
43. Xue Q, Yan D, Chen X, Li X, Kang R, Klionsky DJ, Kroemer G, Chen X, Tang D and Liu J: Copper-dependent autophagic degradation of GPX4 drives ferroptosis. *Autophagy* 19: 1982-1996, 2023.
44. Xue Q, Kang R, Klionsky DJ, Tang D, Liu J and Chen X: Copper metabolism in cell death and autophagy. *Autophagy* 19: 2175-2195, 2023.
45. Waters AM and Der CJ: KRAS: The critical driver and therapeutic target for pancreatic cancer. *Cold Spring Harb Perspect Med* 8: a031435, 2018.
46. Bebbler CM, Müller F, Prieto Clemente L, Weber J and Von Karstedt S: Ferroptosis in cancer cell biology. *Cancers (Basel)* 12: 164, 2020.
47. Park MT, Kim MJ, Suh Y, Kim RK, Kim H, Lim EJ, Yoo KC, Lee GH, Kim YH, Hwang SG, *et al*: Novel signaling axis for ROS generation during K-ras-induced cellular transformation. *Cell Death Differ* 21: 1185-1197, 2014.
48. Viale A, Pettazoni P, Lyssiotis CA, Ying H, Sánchez N, Marchesini M, Carugo A, Green T, Seth S, Giuliani V, *et al*: Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function. *Nature* 514: 628-632, 2014.
49. Brady DC, Crowe MS, Turski ML, Hobbs GA, Yao X, Chaikuad A, Knapp S, Xiao K, Campbell SL, Thiele DJ, *et al*: Copper is required for oncogenic BRAF signalling and tumorigenesis. *Nature* 509: 492-496, 2014.
50. Cui L, Gouw AM, LaGory EL, Guo S, Attarwala N, Tang Y, Qi J, Chen YS, Gao Z, Casey KM, *et al*: Mitochondrial copper depletion suppresses triple-negative breast cancer in mice. *Nat Biotechnol* 39: 357-367, 2021.
51. Wang W, Green M, Choi JE, Gijón M, Kennedy PD, Johnson JK, Liao P, Lang X, Kryczek I, Sell A, *et al*: CD8⁺ T cells regulate tumour ferroptosis during cancer immunotherapy. *Nature* 569: 270-274, 2019.
52. Tang D, Chen X, Kang R and Kroemer G: Ferroptosis: Molecular mechanisms and health implications. *Cell Res* 31: 107-125, 2021.
53. Dai E, Han L, Liu J, Xie Y, Kroemer G, Klionsky DJ, Zeh HJ, Kang R, Wang J and Tang D: Autophagy-dependent ferroptosis drives tumor-associated macrophage polarization via release and uptake of oncogenic KRAS protein. *Autophagy* 16: 2069-2083, 2020.
54. Brewer GJ, Dick RD, Grover DK, LeClaire V, Tseng M, Wicha M, Pienta K, Redman BG, Jahan T, Sondak VK, *et al*: Treatment of metastatic cancer with tetrathiomolybdate, an anticopper, anti-angiogenic agent: Phase I study. *Clin Cancer Res* 6: 1-10, 2000.
55. Turski ML, Brady DC, Kim HJ, Kim BE, Nose Y, Counter CM, Winge DR and Thiele DJ: A novel role for copper in Ras/mitogen-activated protein kinase signaling. *Mol Cell Biol* 32: 1284-1295, 2012.
56. Liu J, Lu Y, Dai Y, Shen Y, Zeng C, Liu X, Yu H, Deng J and Lu W: A comprehensive analysis and validation of cuproptosis-associated genes across cancers: Overall survival, the tumor microenvironment, stemness scores, and drug sensitivity. *Front Genet* 13: 939956, 2022.
57. Hosein AN, Brekken RA and Maitra A: Pancreatic cancer stroma: An update on therapeutic targeting strategies. *Nat Rev Gastroenterol Hepatol* 17: 487-505, 2020.
58. Öhlund D, Handly-Santana A, Biffi G, Elyada E, Almeida AS, Ponz-Sarvisé M, Corbo V, Oni TE, Hearn SA, Lee EJ, *et al*: Distinct populations of inflammatory fibroblasts and myofibroblasts in pancreatic cancer. *J Exp Med* 214: 579-596, 2017.
59. Shinkawa T, Ohuchida K and Nakamura M: Heterogeneity of cancer-associated fibroblasts and the tumor immune microenvironment in pancreatic cancer. *Cancers* 14: 3994, 2022.
60. Biffi G, Oni TE, Spielman B, Hao Y, Elyada E, Park Y, Preall J and Tuveson DA: IL1-induced JAK/STAT signaling is antagonized by TGFβ to shape CAF heterogeneity in pancreatic ductal adenocarcinoma. *Cancer Discov* 9: 282-301, 2019.
61. Xie J, Luo D, Xing P and Ding W: The dual roles of STAT3 in ferroptosis: Mechanism, regulation and therapeutic potential. *J Inflammation Res* 18: 4251-4266, 2025.
62. Chen C, Peng M, Liang S, Li C, Zhu L, Yang Y, Li L and Xue W: Copper homeostasis, emerging central players in cancer immunotherapy. *J Cell Mol Med* 29: e70611, 2025.
63. Oliveri V: Selective targeting of cancer cells by copper ionophores: An overview. *Front Mol Biosci* 9: 841814, 2022.
64. Shimizu M, Koma YI, Sakamoto H, Tsukamoto S, Kitamura Y, Urakami S, Tanigawa K, Kodama T, Higashino N, Nishio M, *et al*: Metallothionein 2A expression in cancer-associated fibroblasts and cancer cells promotes esophageal squamous cell carcinoma progression. *Cancers* 13: 4552, 2021.
65. Blockhuys S and Wittung-Stafshede P: Copper chaperone Atox1 plays role in breast cancer cell migration. *Biochem Biophys Res Commun* 483: 301-304, 2017.
66. Sousa CM, Biancur DE, Wang X, Halbrook CJ, Sherman MH, Zhang L, Kremer D, Hwang RF, Witkiewicz AK, Ying H, *et al*: Pancreatic stellate cells support tumour metabolism through autophagic alanine secretion. *Nature* 536: 479-483, 2016.
67. Zhu Y, Fang S, Fan B, Xu K, Xu L, Wang L, Zhu L, Chen C, Wu R, Ni J, *et al*: Cancer-associated fibroblasts reprogram cysteine metabolism to increase tumor resistance to ferroptosis in pancreatic cancer. *Theranostics* 14: 1683-1700, 2024.
68. Qi R, Bai Y, Li K, Liu N, Xu Y, Dal E, Wang Y, Lin R, Wang H, Liu Z, *et al*: Cancer-associated fibroblasts suppress ferroptosis and induce gemcitabine resistance in pancreatic cancer cells by secreting exosome-derived ACSL4-targeting miRNAs. *Drug Resist Updat* 68: 100960, 2023.
69. Koong AC, Mehta VK, Le QT, Fisher GA, Terris DJ, Brown JM, Bastidas AJ and Vierra M: Pancreatic tumors show high levels of hypoxia. *Int J Radiat Oncol Biol Phys* 48: 919-922, 2000.
70. Shah YM, Matsubara T, Ito S, Yim SH and Gonzalez FJ: Intestinal hypoxia-inducible transcription factors are essential for iron absorption following iron deficiency. *Cell Metab* 9: 152-164, 2009.
71. Peyssonnaud C, Zinkernagel AS, Schuepbach RA, Rankin E, Vaultont S, Haase VH, Nizet V and Johnson RS: Regulation of iron homeostasis by the hypoxia-inducible transcription factors (HIFs). *J Clin Invest* 117: 1926-1932, 2007.
72. Martin F, Linden T, Katschinski DM, Oehme F, Flamme I, Mukhopadhyay CK, Eckhardt K, Tröger J, Barth S, Camenisch G, *et al*: Copper-dependent activation of hypoxia-inducible factor (HIF)-1: Implications for ceruloplasmin regulation. *Blood* 105: 4613-4619, 2005.
73. Trackman PC: Lysyl oxidase isoforms and potential therapeutic opportunities for fibrosis and cancer. *Expert Opin Ther Targets* 20: 935-945, 2016.

74. Dewhirst MW, Cao Y and Moeller B: Cycling hypoxia and free radicals regulate angiogenesis and radiotherapy response. *Nat Rev Cancer* 8: 425-437, 2008.
75. Hubbi ME, Wang CL, Suhail Y, Almasri NL, Xie J, Hollander EE, Kshitiz, Muir A, Stanger BZ and Dang CV: The HIF-2 transcription factor mediates resistance to ferroptosis in pancreatic cancer. *Mol Cell* 86: 1260-1274.e4, 2026.
76. Viswanathan VS, Ryan MJ, Dhruv HD, Gill S, Eichhoff OM, Seashore-Ludlow B, Kaffenberger SD, Eaton JK, Shimada K, Aguirre AJ, *et al*: Dependency of a therapy-resistant state of cancer cells on a lipid peroxidase pathway. *Nature* 547: 453-457, 2017.
77. Hangauer MJ, Viswanathan VS, Ryan MJ, Bole D, Eaton JK, Matov A, Galeas J, Dhruv HD, Berens ME, Schreiber SL, *et al*: Drug-tolerant persister cancer cells are vulnerable to GPX4 inhibition. *Nature* 551: 247-250, 2017.
78. Shanbhag V, Jasmer-McDonald K, Zhu S, Martin AL, Gudekar N, Khan A, Ladomersky E, Singh K, Weisman GA and Petris MJ: ATP7A delivers copper to the lysyl oxidase family of enzymes and promotes tumorigenesis and metastasis. *Proc Natl Acad Sci USA* 116: 6836-6841, 2019.
79. MacDonald G, Nalvarte I, Smirnova T, Vecchi M, Aceto N, Doelemeyer A, Frei A, Lienhard S, Wyckoff J, Hess D, *et al*: Memo is a copper-dependent redox protein with an essential role in migration and metastasis. *Sci Signaling* 7: ra56, 2014.
80. Clark CE, Hingorani SR, Mick R, Combs C, Tuveson DA and Vonderheide RH: Dynamics of the immune reaction to pancreatic cancer from inception to invasion. *Cancer Res* 67: 9518-9527, 2007.
81. Demuyneck R, Efimova I, Naessens F and Krysko DV: Immunogenic ferroptosis and where to find it? *J Immunother Cancer* 9: e003430, 2021.
82. Wen Q, Liu J, Kang R, Zhou B and Tang D: The release and activity of HMGB1 in ferroptosis. *Biochem Biophys Res Commun* 510: 278-283, 2019.
83. Zhu C, Li J, Sun W, Li D, Wang Y and Shen XC: Signaling mechanism of cuproptosis activating cGAS-STING immune pathway. *JACS Au* 4: 3988-3999, 2024.
84. Jung M, Mertens C and Brüne B: Macrophage iron homeostasis and polarization in the context of cancer. *Immunobiology* 220: 295-304, 2015.
85. Ma X, Xiao L, Liu L, Ye L, Su P, Bi E, Wang Q, Yang M, Qian J and Yi Q: CD36-mediated ferroptosis dampens intratumoral CD8+ T cell effector function and impairs their antitumor ability. *Cell Metab* 33: 1001-1012.e5, 2021.
86. Wang W, Kryczek I, Dostál L, Lin H, Tan L, Zhao L, Lu F, Wei S, Maj T, Peng D, *et al*: Effector T cells abrogate Stroma-mediated chemoresistance in ovarian cancer. *Cell* 165: 1092-1105, 2016.
87. Liang C, Zhang X, Yang M and Dong X: Recent progress in ferroptosis inducers for cancer therapy. *Adv Mater* 31: 1904197, 2019.
88. Wang P, Guo W, Liu S, Li S, Li J, Ding B, Yin F, Yang Y, Li X, Cao P, *et al*: Novel Pt@PCN-Cu-induced cuproptosis amplifies α PD-L1 immunotherapy in pancreatic ductal adenocarcinoma through mitochondrial HK2-mediated PD-L1 upregulation. *J Exp Clin Cancer Res* 44: 149, 2025.
89. Jin J, Ma M, Yan B, Qiu B, Lu S, Yang L, Nie Y, Tai S, Yu Z and Teng CB: A SLC31A1-MEK-DNMT1-miR-124 feedback loop contributes to pancreatic cancer progression. *Genes Dis* 10: 654-656, 2023.



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