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Cuproptosis, ferroptosis and PANoptosis in tumor immune microenvironment remodeling and immunotherapy: culprits or new hope

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Abstract

Normal life requires cell division to produce new cells, but cell death is necessary to maintain balance. Dysregulation of cell death can lead to the survival and proliferation of abnormal cells, promoting tumor development. Unlike apoptosis, necrosis, and autophagy, the newly recognized forms of regulated cell death (RCD) cuproptosis, ferroptosis, and PANoptosis provide novel therapeutic strategies for tumor treatment. Increasing research indicates that the death of tumor and immune cells mediated by these newly discovered forms of cell death can regulate the tumor microenvironment (TME) and influence the effectiveness of tumor immunotherapy. This review primarily elucidates the molecular mechanisms of cuproptosis, ferroptosis, and PANoptosis and their complex effects on tumor cells and the TME. This review also summarizes the exploration of nanoparticle applications in tumor therapy based on in vivo and in vitro evidence derived from the induction or inhibition of these new RCD pathways.

Keywords Cuproptosis, Ferroptosis, PANoptosis, TME, Nanoparticles

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Overview of cuproptosis, ferroptosis, and PANoptosis

Occurring recurrently in body tissues, cell death is an irrevocable process that safeguards tissue functionality and morphology. According to cell morphology, biochemistry, and function, the Cell Death Nomenclature Committee divides cell death into accidental and regulated cell death (RCD) [1]. Accidental cell death is a biologically uncontrolled process in response to accidental injury stimuli [2]. RCD is considered an controlled passive process mediated by a series of molecular mechanisms and signaling pathways [3]. Extensive investigations into tumor cells and therapeutic approaches have revealed that RCD-induced cell death

can potentially reshape the immunological properties of the tumor microenvironment (TME), influencing its ability to impede cancer progression and metastasis [4]. The death modes we are familiar with include necrosis, apoptosis, autophagy and necroptosis, which can induce tumor cell death through different molecular mechanisms and signaling pathways to respond to exogenous environments and intracellular disorders. Necrosis refers to an involuntary demise of cells, typically triggered by external harm or stressors like infections, trauma, or ischemia, along with an inflammatory reaction [5]. Conversely, apoptosis represents a deliberate cellular demise, initiated by both internal and external cues, and executed via specific biochemical routes [6]. Autophagy serves as a cellular defense system, ensuring cell survival through the breakdown and reuse of impaired organelles [7]. Pyroptosis, characterized by the death of inflammatory cells, frequently happens during infections by pathogens, resulting in the emission of inflammatory agents [8]. Necroptosis, a regulated form of programmed necrosis, involves a signaling pathway linked to certain proteins, including RIPK3 and MLKL [9]. Each of these forms of RCD has unique biological functions and markers. However, during the treatment process, malignant tumor cells can evolve a variety of mechanisms to evade these RCD pathways, leading to resistance to cancer chemotherapy or to cell death resistance [10]. Therefore, the discovery of new forms of RCD that can counteract the defense mechanism of tumor progression and migration is a new strategy to fight tumor progression. In recent years, the use of emerging modes of cell death to guide cell death has been widely studied. Ferroptosis and cuproptosis are forms of cell death that depend on specific metal ions and are triggered by disorders of iron and copper metabolism, respectively. PANoptosis involves the combined effects of multiple death pathways. All three forms of RCD involves previously unknown cell death mechanisms, characteristics and biomarkers, and their role in tumors has received increasing attention (Fig. 1). In addition, the interaction between cuproptosis and ferroptosis has been reported in cancer. The ferroptosis activators sorafenib and erastin can enhance the copper-based aggregation of lipoylation

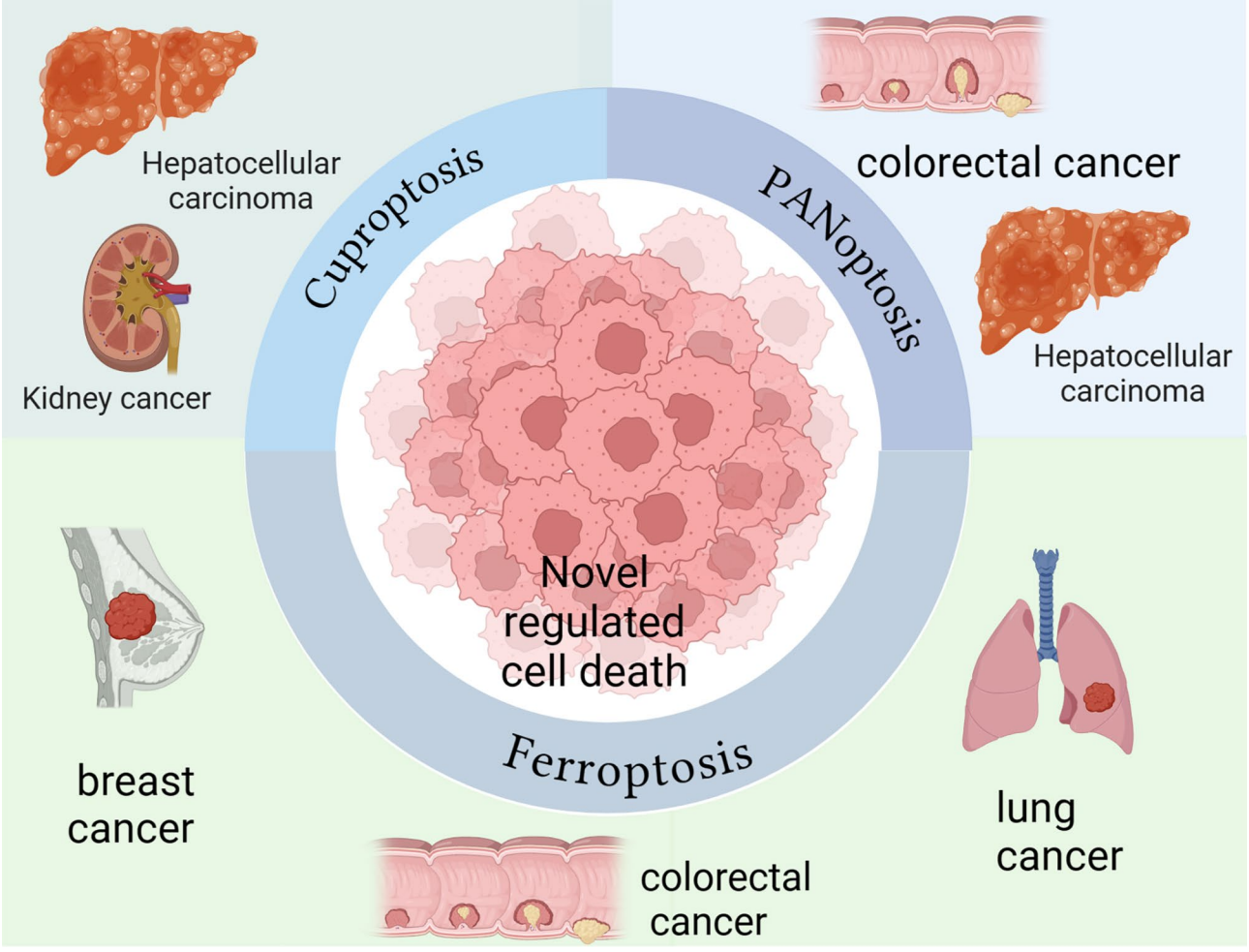

Fig. 1 Diseases related to cuproptosis, ferroptosis, and PANoptosis

proteins, thereby enhancing copper-based sclerosis in HCC by inhibiting mitochondrial matrix-associated protease-induced FDX1 protein degradation and reducing the synthesis of the cellular copper chelator GSH by downregulating the import of cysteine [11]. Copper chelators can attenuate sensitivity to ferroptosis but cannot inhibit other modes of cell death.

Cuproptosis

Cu performs a myriad of crucial functions in biological contexts, functioning as a vital cofactor at numerous enzyme catalytic centers and engaging in extensive processes such as oxidative stress resistance, lipid metabolism, and energy generation [12]. A novel form of Cu-dependent cell death called cuproptosis was first proposed by Tsvetkov et al. in 2022 [13]. Unlike other known cell death modalities, such as apoptosis, necroptosis, and necrosis, cuproptosis is similar to zinc- and Fe-induced death. It is a form of RCD induced by Cu ions.

Copper is an important nutrient that exists in two forms in living organisms, namely, cuprous ions (Cu(I), reduced form) and cupric ions (Cu(II), oxidized form), and is involved in a variety of physiological processes. Dietary Cu(II) is reduced to Cu(I) by the cell surface metalloreductases of the six-transmembrane epithelial antigen (STEAP) family; Cu(I) is then absorbed by epithelial cells in the small intestine via solute carrier family 31 member 1 (SLC31A1), previously called Cu transporter 1 (CTR1) [14]. After intestinal absorption, 95% of the Cu ions are bound to plasma proteins and transported to various organs and tissues through the blood [15]. The liver is the body's primary organ for Cu storage and excretion. Excess Cu is metabolized in the liver, integrated into bile, and excreted through bile secretion, the main route of Cu elimination. The majority of copper is expelled through feces, with a minimal amount being reabsorbed during digestion. The ATPases Cu transporting alpha (ATP7A) and beta (ATP7B) are crucial for the cellular uptake and efflux of Cu [16]. When peripheral Cu levels decrease, ATP7A mobilizes Cu from liver stores into the bloodstream to maintain effective Cu concentrations in the periphery. Inside the cell, ATP7A transports Cu to the trans-Golgi network and vesicles, regulating the subcellular distribution of Cu and targeting various Cu proteins. ATP7B regulates intracellular Cu efflux. In cases of excess Cu, cytoplasmic Cu(I) in hepatocytes binds to metallothionein 1 (MT1), which is then transferred to the bile canaliculi membrane to excrete excess Cu from the body [17, 18].

In experiments investigating Cu ion carrier-induced cell death regulation in mitochondrial respiration, whole-genome CRISPR/Cas9 functional loss screening has elucidated specific metabolic pathways mediating cuproptosis. Seven key genes that promote cuproptosis have been identified: ferredoxin 1 (*FDX1*) and lipoyltransferase 1 (*LIPT1*), which are involved in the lipoic acid pathway; lipoic acid synthase (*LIAS*); dihydrolipoamide dehydrogenase (*DLD*); dihydrolipoamide S-acetyltransferase (*DLAT*); pyruvate dehydrogenase E1 subunit alpha 1 (*PDHA1*); and pyruvate dehydrogenase E1 subunit beta (*PDHB*) [19]. Knocking out these genes inhibited the cell death induced by $CuCl_2$ and the Cu ion carrier elesclomol (ES). In essence, cuproptosis involves the continuous accumulation of Cu^{2+} in mitochondria, which directly binds to the lipoyl components of the tricarboxylic acid (TCA) cycle, affects FDX1 regulation of protein thiols, and causes the aggregation of lipoylated proteins, Fe-sulfur (S) cluster protein instability, acute protein toxicity stress, and cell death [15] (Fig. 2). This process does not directly involve the electron transport chain (ETC) but affects mitochondrial respiration, inducing cell death. FDX1 and protein thiols play crucial regulatory roles in Cu ion carrier-induced cell death, with FDX1 encoding a reductase that reduces Cu^{2+} to more toxic Cu^{+} and is a direct target of the Cu ion carrier ES. FDX1 regulatory factor of protein thiols, and its knockout can lead to the loss of protein thiols [20].

Protein lipoylation occurs only in important components of the pyruvate dehydrogenase complex, such as dihydrolipoamide S-succinyltransferase (DLST) and DLAT, where protein lipoylation modifications are needed to regulate and perform enzyme functions. Cu^{2+} directly binds to lipoylated proteins [20, 21], causing oligomerization of lipoylated DLAT. Fe-S proteins are necessary auxiliary factors for enzymes involved in the ETC and other biochemical processes. The aggregation of mitochondrial enzymes may disrupt these Fe-S cluster proteins [22]. Thiol proteins are associated with various human tumors, and cell lines highly expressing thiol proteins are sensitive to cuproptosis [23]. ES-induced cell death is not caused by the interaction between FDX1 and ES but rather between FDX1 and the ES-Cu^{2+} complex, suggesting that the binding of FDX1 to the ES-Cu^{2+} complex completely oxidizes FDX1, inhibiting Fe-S cluster biosynthesis. Importantly, ES and Cu^{2+} alone cannot oxidize FDX1, confirming the role of the Cu^{2+} complex in the anticancer activity of ES and its analogs [24]. Studies have shown that the therapeutic effects of ES on tumors depend on FDX1 levels, increased mitochondrial respiration rates, and Cu levels.

Copper ions play pivotal roles in cell activities. Upon entering cells, they integrate with chaperone proteins, which facilitate their intricate transport to diverse cellular sections and thereby modulating numerous physiological functions. The Cu chaperone for superoxide dismutase (CCS) transfers Cu ions to specific proteins, including superoxide dismutase 1 (SOD1), which requires Cu as a cofactor [25]. SOD1 catalyzes the conversion of

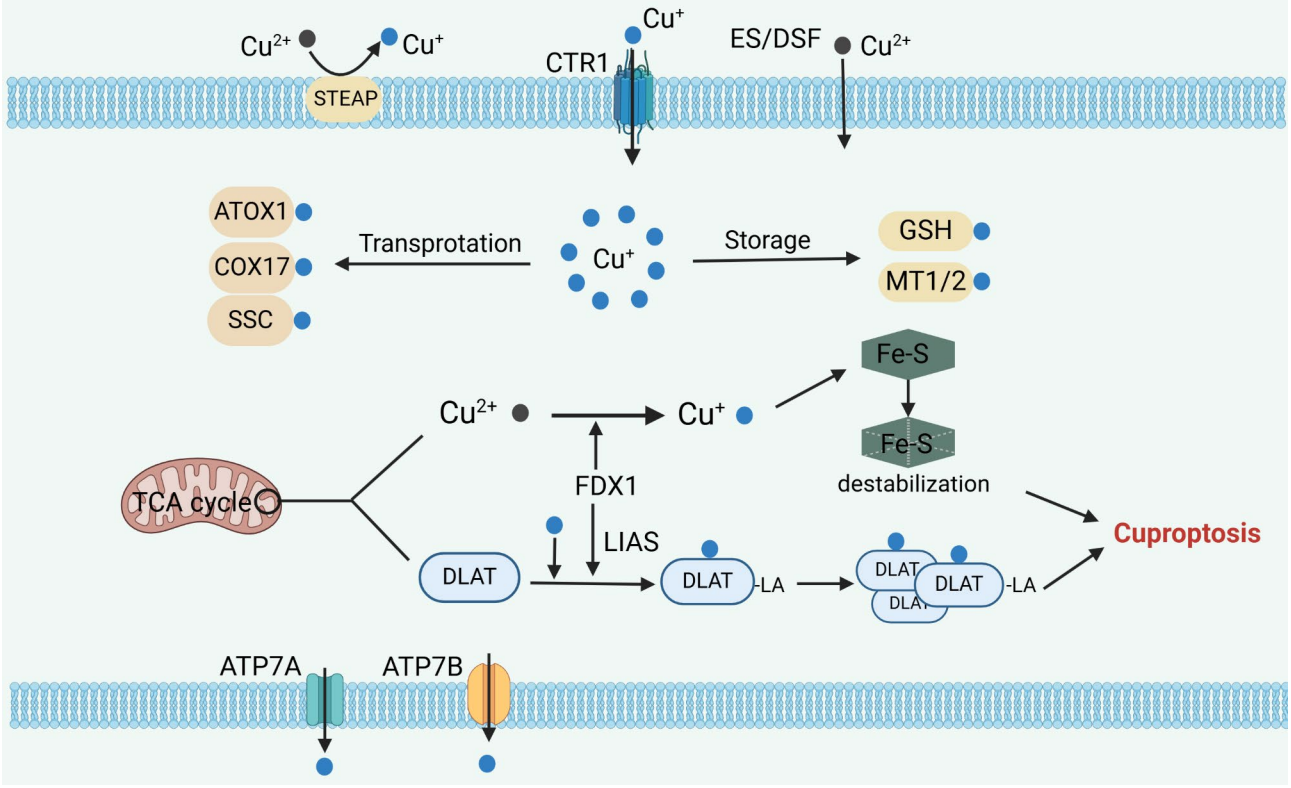

Fig. 2 Pathways mediating copper (Cu) metabolism. Cu(II) (Cu^{2+}) must be converted to Cu(I) (Cu^{+}) by metalloreductases of the six-transmembrane epithelial antigen (STEAP) family before being absorbed by intestinal epithelial cells. Elesclomol (ES) binds to Cu^{2+} in the extracellular environment and transports it into intracellular compartments. Cu^{+} is primarily transported into cells via solute carrier family 31 member 1 (SLC31A1), previously called Cu transporter protein 1 (CTR1). In the cytoplasm, the Cu chaperone superoxide dismutase 1 (SOD1) delivers Cu to specific proteins, which are then transported to the trans-Golgi apparatus by the antioxidant 1 Cu chaperone (ATOX1) and to mitochondria by the cytochrome c oxidase Cu chaperone COX17 (COX17). Excess intracellular Cu ions can be sequestered by three key molecules: metallothioneins 1 (MT1) and 2 (MT2) and glutathione (GSH). Cu accumulation primarily leads to cuproptosis through mitochondrial protein toxicity stress mediated by ferredoxin 1 (FDX1). While FDX1 reduces Cu^{2+} to Cu^{+}, promoting the lipidation (LA) and aggregation of enzymes involved in the mitochondrial tricarboxylic acid (TCA) cycle, particularly dihydrolipoamide S-acetyltransferase (DLAT), it also causes instability of Fe–S cluster proteins

superoxide radicals ($O2^{\bullet-}$) to oxygen (O_2) and hydrogen peroxide (H_2O_2), helping protect cells from oxidative stress. Cu plays essential roles in mitochondrially encoded cytochrome c oxidase I (MT-CO1) and II (MT-CO2), providing the necessary catalytic activity to facilitate the redox reactions critical for ATP production. The cytochrome c oxidase Cu chaperone COX17 (COX17) transfers Cu(I) from the cytoplasm to cytochrome c oxidase assembly protein synthesis of cytochrome c oxidase 1 (SCO1) and 2 (SCO2) on the inner mitochondrial membrane, along with cytochrome c oxidase assembly factors COX16 (COX16) and 6 (COA6), promoting Cu transfer from SCO1 and SCO2 to MT-CO2 [26, 27]. Similarly, once intracellular copper levels exceed the limits of normal homeostatic regulation, creating an imbalance in copper homeostasis, either due to excessive accumulation or transport problems, cytotoxic effects may be triggered, leading to oxidative stress, cell death and tissue damage [28]. The content of Cu in the normal human body is approximately 100–200 mg [29]. Elevated levels of copper are frequently observed in the cancerous tissues and/or blood of individuals with a range of cancers, such as breast, lung, gastrointestinal, oral, thyroid, gallbladder, cervical, ovarian, kidney, and prostate cancers [30]. Free labile copper ions in cells can undergo Fenton-like reactions to produce reactive oxygen species (ROS), leading to the destruction of iron–sulfur cofactors. Proteins are crucial in reducing the buildup of Cu (I) within cells by attaching to and capturing surplus copper ions. Cu plays a crucial role in the development and spread of tumors; yet, the molecular processes behind copper-triggered toxicity and cell death are still not understood. Notably, two important antioxidant peptides, metallothioneins and glutathione (GSH), play important roles in this detoxification mechanism.

The development of Cu-dependent tumors may involve several mechanisms described here. Typically, cancer cells require higher levels of copper than normal cells to maintain energy. At the same time, increased Cu concentrations can hinder protea- some activity, affecting

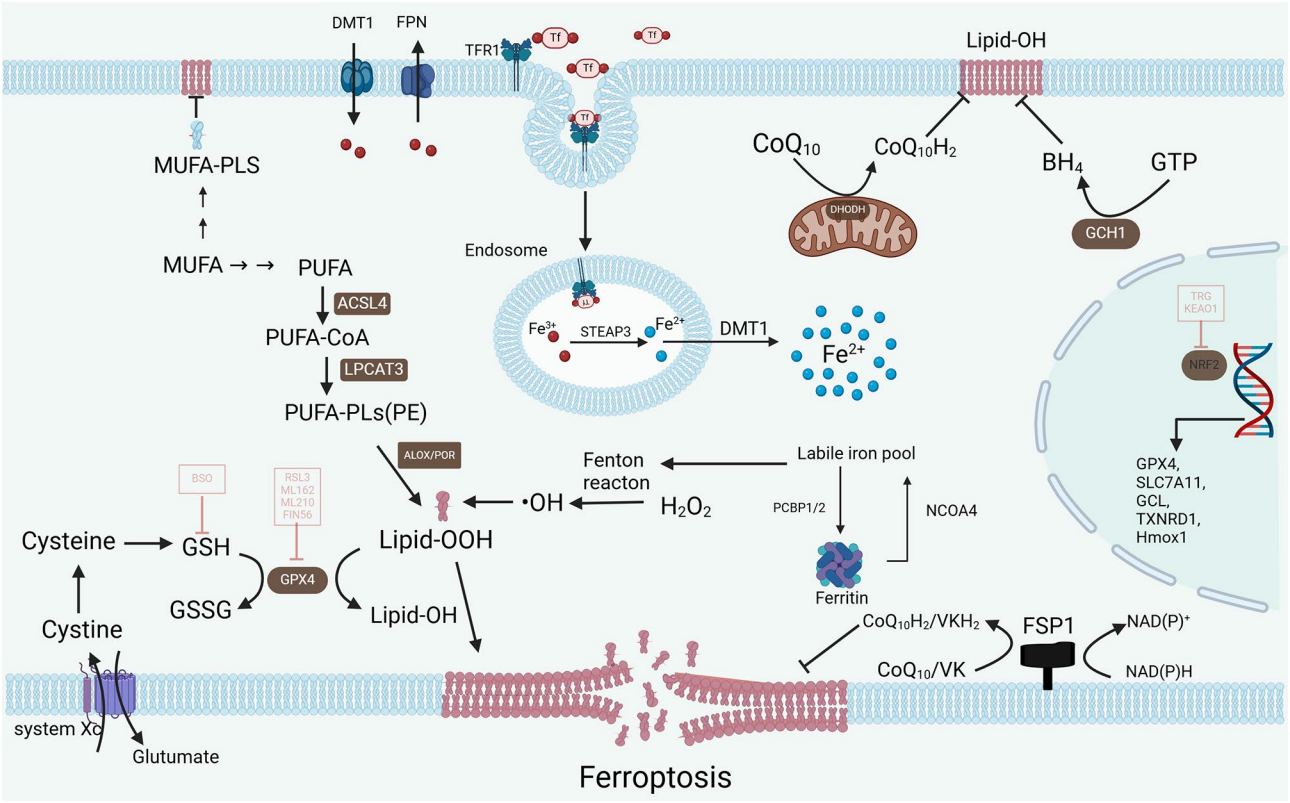

Fig. 3 Schematic diagram of the ferroptosis mechanism based on lipid peroxidation. Ferroptosis is initiated by both nonenzymatic and enzymatic processes. Nonenzymatic processes include the Fenton reaction, in which iron (Fe) reacts with hydrogen peroxide (H_2O_2) to form free radicals. Various enzymes and proteins drive ferroptosis by increasing Fe utilization and enhancing free radical formation, and they play important roles in PUFA biosynthesis and oxidation (ACSL4 and ALOX). Conversely, ferroptosis is inhibited by several enzymes and cofactors with antioxidant functions (GPX4, GSH, FSP1, CoQ10, and BH4) and the system Xc−cystine/glutamate reverse transporter (SLC7A11 and SLC3A2), which take up the cysteine required for antioxidant enzyme biosynthesis. Abbreviations: Fe^{2+}: ferrous Fe; Fe^{3+}: ferric Fe; LPCAT3: lysophosphatidylcholine acyltransferase 3; GSSG: oxidized glutathione; GSH: reduced glutathione; GPX4: glutathione peroxidase 4; GTP: guanosine triphosphate; BH_4: tetrahydrobiopterin; GCH1: GTP cyclohydrolase 1; LIP: labile Fe pool; DMT1: divalent metal transporter 1; TF: transferrin; TFR1: transferrin receptor 1; FPN: ferroportin; ROS: reactive oxygen species; PL-OH: phospholipid alcohol; lipid-OOH: phospholipid hydroperoxide; PUFA: polyunsaturated fatty acid; MUFA: monounsaturated fatty acid; ACSL4: acyl-CoA synthetase long-chain family member 4; CoA: coenzyme A; LPCAT: lysophosphatidylcholine acyltransferase; PLS: phospholipid; LOX: lipoxygenase; POR: cytochrome P450 oxidoreductase; PUFA-OOH: polyunsaturated fatty acid peroxide; system Xc−: cystine/glutamate reverse transporter; SLC7A11: solute carrier family 7 member 11; SLC3A2: solute carrier family 3 member 2; CoQ_{10}: coenzyme Q_{10}; $CoQ_{10}H_2$: reduced coenzyme Q10; FSP1: ferroptosis suppressor protein 1; NRF2: nuclear factor E2-related factor 2; BSO: buthionine sulfoximine; GCL: glutamate-cysteine ligase; TXNRD1: thioredoxin reductase 1; HMOX1: heme oxygenase 1; NCOA4: nuclear receptor coactivator 4; PCBP1/2: poly(rC)-binding protein 1/2; PE: phosphatidylethanolamine; NAD(P)H: reduced nicotinamide adenine dinucleotide phosphate; $NAD(P)^+$: oxidized nicotinamide adenine dinucleotide phosphate; VK: vitamin K; VKH2: reduced vitamin K

the breakdown of proteins and causing the buildup of misfolded proteins [32, 33]. Excess copper enhances the ubiquitin-proteasome pathway, causing the degradation of proteins such as the tumor suppressor p53 (TP53), consequently disrupting its operational integrity [31]. Copper plays a pivotal role in oncogenic signaling cascades, particularly in pathways such as RAS-RAF-MEK-E RK and PI3K - AKT-mT OR, which are essential for tumor growth. Additionally, copper stimulates autophagy, thereby supporting the survival and proliferation of cancer cells, as demonstrated in models of KRAS G12D - mutant lung adenocarcinoma [34]. The Cu enzymes lysyl oxidase (LOX) and lysyl oxidase like-1 (LOXL1/ LOXL) are associated with the invasion and metastasis of various cancers [35–37]. The process enhances immune evasion by increasing copper levels, which can hinder anticancer immunity through higher expression of the immune checkpoint receptor PD-L1, also known as CD274 [38]. These findings illustrate the multiple functions of copper in orchestrating various aspects of cancer development, such as uncontrolled cell growth, enhanced blood vessel formation, increased met- astatic potential, metabolic disruption, the ability to fuel inflammation within tumors, and the ability to promote immune system evasion.

Detection methods for cuproptosis

Biomarker detection Copper-dependent thioesterification: Copper ions can trigger the thioesterification of mitochondrial lipoylated proteins, essential for cupropto-

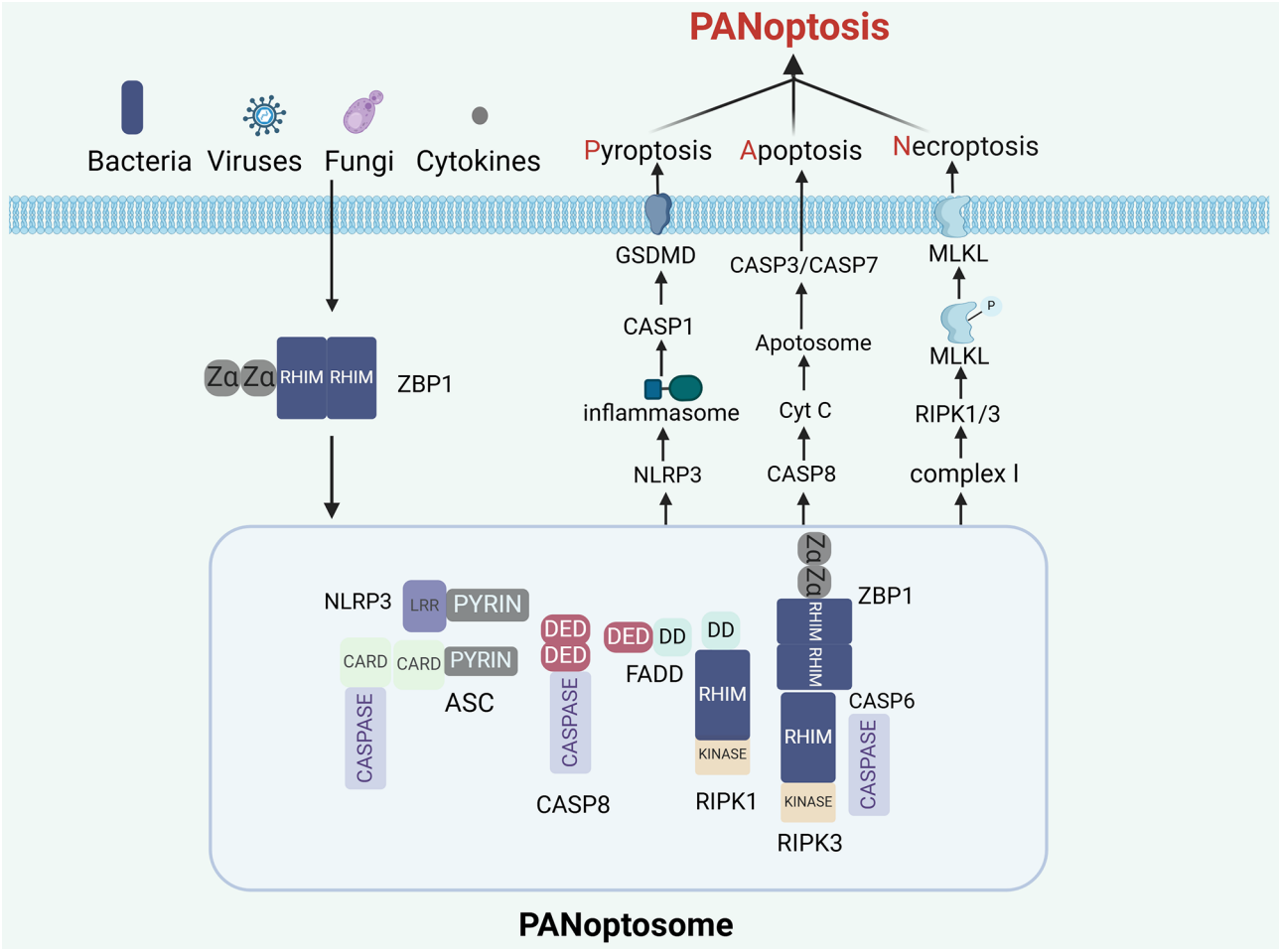

Fig. 4 PANoptosis processes involving ZBP1 and its complexes. PANoptosis is a regulated form of cell death triggered by specific signals, exhibiting key features of apoptosis, pyroptosis, and necroptosis, but none of these can characterize it alone. A large protein complex (PANoptosome), comprising sensors, adaptors, and catalytic effectors, assembles via interacting domains to initiate PANoptosis. Abbreviations: ASC: apoptosis-associated speck-like protein with a caspase recruitment domain; CASP: caspase; FADD: Fas-associated death domain-containing protein; MLKL: mixed lineage kinase domain-like protein; NLRP3: NOD-like receptor containing pyrin domain 3; RIPK: receptor-interacting serine/threonine-protein kinase; ZBP1: Z-DNA binding protein 1

sis. Protein thioesterification, including dihydrolipoamide dehydrogenase (DLD), pyruvate dehydrogenase complex (PDC), α-ketoglutarate dehydrogenase complex (OGDC), and branched-chain α-ketoacid dehydrogenase complex (BCKDC), is identifiable through mass spectrometry; as an alternative, specific antibodies in western blotting can verify these protein alterations.

Dysfunction of iron-sulfur cluster proteins: The detrimental impact of copper may hinder the function of iron-sulfur cluster proteins, such as mitochondrial enzymes that have Fe-S clusters vital for cell energy mechanisms. Evaluating the activity and expression levels of iron-sulfur cluster proteins, such as ACO2 and SDHB, might indirectly reflect the cellular effects of copper toxicity.

Reduced mitochondrial membrane potential: Mitochondrial damage from copper toxicity usually leads to a lowered mitochondrial membrane potential.Fluorescent dyes such as JC-1, TMRE, or TMRM are suitable for detection.

Release of Cytochrome c: Damage to mitochondria can trigger the movement of cytochrome c from mitochondria to the cytoplasm, thereby triggering subsequent cell death signals. The technique of Western blotting or immunofluorescence staining serves to identify alterations in the positioning of cytochrome c.

ROS generation: mitochondrial dysfunction caused by copper ions often leads to the creation of reactive oxygen species (ROS), and an excess of ROS can cause cell death.Probes such as DCFDA and MitoSOX are capable of detecting ROS concentrations inside a cell.

Metabolic index detection Changes in intermediaries of the citric acid cycle: Copper's toxic effects affect mitochondrial function and may alter metabolites in the citric acid cycle (TCA cycle).

Table 1 Summary of the detection methods for cuproptosis

Related metabolic processes	Detection Indicator
Cell morphology	Plasma membrane rupture
	Mitochondrial rupture
Metaboli index	Cu ion accumulation
	Alpha-ketoglutarate accumulation
	Decreased succinic acid
Nucleic acid amplification testing	ROS
	Superoxide anion radical
	Hydrogen peroxide
Glutathione metabolism	FDX1
	DLAT
	LIAS
Protein detection	HSP70 reduction
	Increased Fe-S

Employing liquid chromatography-mass spectrometry (LC) or gas chromatography-mass spectrometry (GC) facilitates the analysis of fluctuations in TCA cycle intermediates such as citrate, α-ketoglutarate, and succinate, reflecting the impact of copper ions on mitochondrial metabolism.

Mitochondrial respiratory chain dysfunction: Copper toxicity may affect the electron transport chain, thereby changing cellular energy metabolism. Detection of the cellular oxygen consumption rate (OCR) and ATP production can reflect the metabolic state of mitochondria.

Lipid peroxidation outcomes: The oxidative stress from copper ions triggers lipid peroxidation, resulting in the formation of metabolites such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), detectable via chromatographic or immunological methods.

Ratio of lactate to pyruvate: In cuproptosis, cells may rely greatly on glycolysis due to mitochondrial complications. Variations in the lactate to pyruvate ratio may indicate this metabolic alteration.

Levels of Glutathione (GSH): This protein is vital as an antioxidant inside cells. Copper-induced oxidation may result in decreased GSH levels, and changes in the ratio of GSH to oxidized glutathione (GSSG) could signal the state of oxidative stress in cells (Table 1).

Ferroptosis

Ferroptosis is an Fe-dependent form of RCD that occurs due to the accumulation of lipid ROS within cells, leading to peroxidation damage to the cell membrane. It was first reported and named by Dixon et al. in 2012 [39]. In various types of tumors, ferroptosis can promote tumor cell death. Clinically, enhancing the effects of therapeutic drugs on tumors by inducing ferroptosis in tumor cells can help overcome drug resistance. The key mechanisms involved in ferroptosis are mainly related to Fe metabolism, lipid metabolism, the cystine–glutamate reverse transporter (system Xc^-)/GSH/GSH peroxidase 4 (GPX4) pathway, and the TP53 gene regulation pathway. Key associated organelles include mitochondria, the endoplasmic reticulum, and lysosomes (Fig. 3) [40]. In addition, miRNAs target different ferroptosis players in different pathophysiological conditions (Table 6).

Fe accumulation

Ferroptosis relies on Fe accumulation, and proteins that maintain Fe homeostasis are crucial in regulating ferroptosis. Fe ions (Fe^{2+}) are key inducers of lipid peroxidation and ferroptosis. Fe transport proteins, such as transferrin (TF), increase Fe^{2+} levels through Fe uptake, which is mediated by Fe protein autophagy or lysosomal degradation, among other Fe metabolism pathways [41]. Proteins such as TF, heme oxygenase 1 (HOMX1/HO-1), and the TF receptor (TFRC) help regulate ferroptosis by influencing intracellular Fe levels [42]. Increased cellular iron(II) levels facilitate lipid peroxide buildup via dual mechanisms. The first is by inducing ROS production through Fe-dependent Fenton reactions, where Fe^{2+} ions catalyze the production of hydroxyl radicals and hydroxide ions, among other ROS, via their redox activity, leading to the direct generation of phospholipid hydroperoxides (PLOOHs). The second mechanism involves the activation of Fe-dependent enzymes, including Fe-containing lipoxygenase (LOX) and cytochrome P450 oxidoreductase (POR), which catalyze PLOOH production, thereby promoting ferroptosis [43]. Studies have shown that Fe chelators can inhibit ferroptosis by reducing Fe levels, further confirming the crucial role of excess Fe in ferroptosis [44, 45].

Lipid peroxidation

In lipid metabolism pathways, free polyunsaturated fatty acids (PUFAs) are substrates for synthesizing lipid signaling molecules and are highly sensitive to ROS-induced peroxidation reactions. In the lipid bilayer, phospholipids containing polyunsaturated fatty acid chains (PUFA-PLs) undergo oxidative damage when a hydrogen atom within their double bonds is lost, resulting in the formation of reactive phospholipid hydroperoxyl radicals upon interaction with oxygen. This process leads to the removal of another hydrogen from another PUFA, forming PLOOH [46]. If PLOOHs are not reduced back to the corresponding alcohol by GPX4, their excess accumulation may ultimately disrupt the integrity of cell membranes, leading to organelle and/or cell membrane rupture [47]. Lysophosphatidylcholine acyltransferase 3 (LPCAT3) and acyl-CoA synthetase long-chain family member 4 (ACSL4) help to activate the transmembrane properties of PUFAs and integrate them into phospholipids, making them sensitive factors in inducing ferroptosis [48]. PUFAs can also undergo site-specific oxidation catalyzed by LOX, leading to ferroptosis [49].

The system Xc−/GSH/GPX4 ferroptosis defense pathway

System Xc^- is composed of a light-chain subunit (solute carrier family 7 member 11 [SLC7A11]) and a heavy-chain subunit (solute carrier family 3 member 2 [SLC3A2]). Since it functions to exchange glutamate for cysteine across the cell membrane at a 1:1 ratio, extracellular glutamate levels affect system Xc^- function [50]. High extracellular glutamate concentrations inhibit system Xc^- and induce ferroptosis, potentially explaining the toxic effects of accumulated glutamate in the nervous system [39]. Under physiological conditions, the accumulation of extracellular glutamate can act as a natural trigger of ferroptosis.

Owing to its combination of cysteine and glutamate, GSH has the highest prevalence as a cellular reducing agent in mammals, playing a vital role in Fe-S cluster formation. GPX4 is a key inhibitory factor for ferroptosis and possesses peroxidase activity. Its abnormal expression is associated with carcinogenesis. GPX4 acts as a GSH-dependent peroxidase, reducing toxic PL-PUFA hydroperoxides into nontoxic and nonlethal PUFA-PL alcohols to counteract lipid peroxidation. The limited availability of cysteine restricts GSH biosynthesis, and some cells use the transsulfuration pathway to synthesize cysteine from methionine, bypassing the cysteine/glutamate reverse transport of system Xc^-'s requirement for cysteine intake. Consequently, these cells exhibit inherent resistance to ferroptosis activated by system Xc− inhibitors.

TP53 gene regulation pathway

Studies show that TP53 plays a twofold part in managing ferroptosis. From a mechanistic perspective, upon activation, TP53 binds directly to the SLC7A11 promoter or interacts with ubiquitin-specific peptidase 7, reducing histone H2B monoubiquitination on the promoter, thus decreasing SLC7A11 expression and lessening cysteine uptake (thereby decreasing GSH synthesis), which promotes ferroptosis [51–53]. Conversely, TP53 impedes ferroptosis through its direct interaction with dipeptidyl peptidase 4 (DPP4), blocking its attachment to nicotinamide adenine dinucleotide phosphate (NADP+) oxidase 1 (NOX1) and stopping the latter from initiating ROS production. This mechanism triggers the production of cyclin-dependent kinase inhibitor 1 A (CDKN1A), which in turn boosts the fresh production of intracellular GSH and stimulates the production of transglutaminase 2 (TGM2), subsequently elevating the amounts of intracellular $NADP^+$ and GSH [54, 55]. Additionally, p53 enhances ferroptosis by regulating the expression of spermine/spermidine N1-acetyltransferase 1 (SAT1) and its role in cellular metabolism. SAT1 promotes the oxidation of arachidonic acid (AA) to generate lipid peroxides by promoting the activity of arachidonic acid 15-lipoxygenase (ALOX15) [51, 56]. Altered forms of p53 serve varied functions in the process of ferroptosis. The P47S form of p53 enhances ferroptosis resistance through elevated levels of CoA and GSH [57]. Altered forms of p53 serve varied functions in the process of ferroptosis. Mutants of mouse p533KR (K117R, K161R, and K162R) no longer respond to traditional DNA damage, yet retain the ability to suppress SLC7A11, triggering ferroptosis and hindering tumor expansion [58]. Nonetheless, mutants of mouse p534KR (K98R, K117R, K161R, and K162R) fail to suppress SLC7A11 and trigger ferroptosis [59].

Oncogene activation also renders cancer cells susceptible to ferroptosis

Deactivating tumor suppressor genes generally promotes resistance to ferroptosis. The cadherin 1 (CDH1/E-cadherin)-neurofibromin 2 (NF2)-Hippo signaling pathway is a prominent example of such a loop. Unlike other tumor suppressor genes, this tumor suppressor axis inhibits ferroptosis [60]. The CDH1-mediated cell–cell interactions, which act in an NF2-dependent manner, stimulate the Hippo tumor suppressor pathway, suppress the transcriptional processes of YAP and TAZ, and subsequently reduce the expression of ferroptosis-enhancing components, thereby arresting ferroptotic cell death. Hence, when any member of the CDH1-NF2-Hippo signaling cascade is compromised, it leads to increased levels and/or functionality of YAP or TAZ, rendering cancer cells or tumors harboring pathway mutations, such as NF2-mutant mesothelioma, highly vulnerable to ferroptotic cell death [61].

Detection of ferroptosis

(1) Observation of cell and mitochondrial morphology: During ferroptosis, cells typically exhibit shrinkage, cytoplasmic swelling, membrane rupture, chromatin condensation, and DNA fragmentation. In addition, their mitochondria exhibit atrophy, increased membrane density, fewer or no cristae, and outer membrane rupture. Since ferroptosis leads to cell death, detecting cell viability is common.
(2) Fe ion detection: Cellular Fe accumulation is a typical sign of ferroptosis, and Fe^{2+} accumulation can specifically increase oxidative stress levels.
(3) Lipid peroxidation: Indicators of lipid peroxidation in ferroptosis include changes in GSH synthesis, the levels of lipid peroxidation products (malonaldehyde and peroxidated lipids), and unrestricted lipid peroxidation, which is a distinctive characteristic of ferroptosis.
(4) GSH metabolism: GSH content decreases during ferroptosis, and GSH metabolism helps regulate

Table 2 Summary of detection methods for ferroptosis

Related metabolic processes	Detection Indicator
Cell morphology	Cell shrinkage and membrane rupture
	Cytoplasmic swelling
	Chromatin condensation DNA fragmentation
Iron metabolism	Iron ions
	Ferrous ions
Lipid peroxidation	MDA
	LPO
Reactive oxygen species	ROS
	Superoxide anion radical
	Hydrogen peroxide
	SOD
Glutathione metabolism	GSH
	T-GSH
	GSH-PX
	GR
	GLU
	Cys
Detection of different key proteins	Caspase-1
	Caspase-8
	p-/t-MLKL

ferroptosis (GSH, GSH peroxidases, glutathione-disulfide reductase [GSR/GR], glutamate, and cysteine).

(5) ROS: Ferroptosis is often accompanied by an increase in ROS. ROS and lipid ROS play crucial roles in ferroptosis, and studies have reported that increased superoxide dismutases can reduce ROS levels in the body. Fe accumulation in cells may inhibit the antioxidant system, and Fe may directly produce excess ROS through the Fenton reaction, increasing oxidative damage. Therefore, ROS detection is also common.

(6) Ferroptosis genes: In cells or tissues undergoing ferroptosis, *GPX4* and hypoxia-inducible factor 1 subunit alpha inhibitor (*HIF1AN*/*FIH1*) expression is downregulated, whereas *COX2, ACSL4,* prostaglandin-endoperoxide synthase 2 (*PTGS2*), and *NOX1* expression is upregulated. Therefore, ferroptosis can be indirectly detected by determining the mRNA levels of these genes via quantitative PCR or their protein levels via western blotting (Table 2).

PANoptosis

Since the discovery and description of "PANoptosis" in 2019, the number of research articles published on this topic has rapidly increased [62]. PANoptosis, a pivotal player in innate immunity, strongly contributes to various infections and inflammatory disorders. Recently, investigations have revealed the significant role of PANoptosis in the etiology of various malignancies [63–70]. The PANoptosome is formed by upstream receptors and molecular signals that control PANoptosis. The formation of PANoptosomes results in cell death through the coordinated induction of pyroptosis, apoptosis, and necroptosis [71].

Pyroptosis is a type of regulated cell death marked by inflammatory reactions that usually take place following the formation and stimulation of inflammasomes. This form of cell death is characterized by cellular swelling, the creation of pores in the cell membrane, membrane rupture, and the discharge of cellular contents. Pyroptosis is considered a classic pathway for inflammatory programmed cell death (PCD) [72]. It primarily occurs through the activation of inflammasomes within the body, which in turn activate the caspase protein family (such as caspase-1/3/4/5/8/11) or granzymes (such as granzyme A/B) to cleave and activate gasdermin proteins. After being triggered, the gasdermin proteins move to the cell membrane, damaging its structural stability and eventually creating openings that release the cellular contents. This mechanism triggers pyroptosis and initiates inflammation [73].

Apoptosis is a caspase-mediated, noninflammatory pathway distinguished by the generation of apoptotic bodies. Cytomorphologically, apoptotic cells display a characteristic pattern featuring cell shrinkage, distinct nuclear DNA fragments, condensed chromatin, and the emergence of apoptotic bodies (ApoBDs), all while preserving the integrity of the cellular membrane [74–76]. Factors such as pathogen invasion, DNA injury, hypoxia, and the presence of specific cancer-related proteins can trigger the process of apoptosis [77, 78]. Apoptosis, a fundamental PCD process, is triggered via two distinct routes, the extrinsic and intrinsic pathways, highlighting its remarkable biological conservation. The intrinsic mitochondrial pathway is regulated primarily by Bcl-2 family proteins. Under cellular stress, BH3-only proteins, critical initiators of apoptosis and part of the Bcl-2 family, induce the activation of the effector proteins BAX and BAK. This activation promotes mitochondrial outer membrane permeabilization (MOMP) and the liberation of cytochrome c (Cyt c) [79–82]. Subsequently, cytochrome c (Cyt c) combines with Apaf-1 and dATP in the cytoplasm to form a structure called the apoptosome [82–84]. The formation of the apoptosome induces the activation of caspase-9 (CASP9), which subsequently activates and cleaves caspase-3/6/7, promoting proteolytic cleavage of various proteins and ultimately leading to cell apoptosis [85, 86]. The extrinsic apoptotic route involves death receptors, such as FADD and TRADD, which possess death domains. Upon binding to specific ligands, these receptors initiate this process by recruiting and activating caspase-8. This subsequently results in the formation of the death-inducing signaling complex

(DISC), followed by the caspase-8-mediated activation of executioner caspases or the activation of the intrinsic apoptotic pathway [87].

Unlike apoptosis, necroptosis occurs independently of caspases. The morphological features of necroptosis include cell membrane disruption, cellular and organelle swelling, and chromatin fragmentation [88–90]. Concurrently, necroptotic cell death results in the release of a cocktail of DAMPs, proinflammatory cytokines, and chemokines, collectively sparking an inflammatory cascade within the organism [91]. Necroptosis is predominantly mediated by receptor-interacting protein kinase 1 (RIPK1), receptor-interacting protein kinase 3 (RIPK3), and mixed lineage kinase domain-like protein (MLKL). This form of lytic cell death operates independently of caspases [92, 93]. Tumor necrosis factor (TNF) is a key regulator of cell survival, apoptosis, and necroptosis. Research on TNF signaling is crucial for identifying pathways involved in necroptosis, as TNF plays a significant role in inflammation induced by infection or injury [94, 95]. The key players in the necroptosis signaling pathway include RIPK1, RIPK3, and MLKL [96]. In the absence of apoptosis, particularly under conditions of caspase-8 inhibition, receptor-interacting protein kinase 1 (RIPK1), RIPK3, mixed lineage kinase domain-like protein (MLKL), FADD, and procaspase-8 assemble into a complex termed Complex IIb, also referred to as the necrosome, via the TNF or Toll-like receptor signaling pathways. RIPK3 phosphorylates MLKL and promotes its oligomerization, facilitating its translocation to the cell membrane, which is a crucial molecular mechanism in necroptosis [85] Necroptosis serves as a "fail-safe" mechanism in which standard apoptosis pathways are inhibited due to caspase deficiency or the inhibition of caspase activity. During infections or when oncogenic mutations hinder caspase activation, this alternative cell death mechanism safeguards the continuation of cell death [93, 97].

In a 2019 study, Professor Kanneganti's team coined the term PANoptosis to refer to the phenomenon of simultaneously regulating pyroptosis, apoptosis, and necroptosis [98–100]. PANoptosis, an innate immune, lytic, and inflammatory cell death mechanism, involves caspases and RIP kinases. Its regulation occurs through the PANoptosome complex (Fig. 4). Single-cell analysis revealed the presence of PANoptosome complexes under certain conditions [101]. The interactions between various protein domains involved in PANoptosis can be categorized into three classes: Sensor proteins have sensing domains, such as Z-DNA binding protein 1 (ZBP1); adapter proteins with caspase recruitment domains, such as apoptosis-associated speck-like protein (ASC); and effector proteins with catalytic domains, including RIPK1, RIPK3, and caspase-1/8 [102]. To date, four types of PANoptosome complexes have been identified, including the ZBP1-PANoptosome, AIM2-PANoptosome, RIPK1-PANoptosome, and NLRP12-PANoptosome [64, 65, 103, 104]. The composition of the PANoptosome is contingent upon specific triggering factors but typically encompasses Z-DNA binding protein 1 (ZBP1), absent in melanoma 2 (AIM2), RIPK3, RIPK1, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), Fas-associated protein with death domain (FADD), and CASP8, as well as essential effectors of the pyroptosis, apoptosis, and necroptosis pathways [105].

PANoptosis and its relationship with cancer have garnered considerable research interest in recent years. Molecular clustering, derived from the analysis of PANoptosis, holds great potential in predicting patient prognosis and discerning tumor microenvironment traits. Liu et al. developed a predictive model, the PANoptosis-associated risk score (PANS), utilizing genes intricately linked to this cellular process. This score can assist in the comprehensive analysis of the correlations between PANS and gastric cancer prognosis, the tumor microenvironment (TME), immune therapy effectiveness, and chemotherapy drug sensitivity [106]. Zhong et al. [107] identified 14 PANoptosis-related gene signatures that can effectively predict the prognosis of melanoma patients. Furthermore, they analyzed the underlying reasons for prognostic differences through immune infiltration, tumor mutation burden analysis, immune therapy response, and drug sensitivity assays. Extensive examination of particular cancer cell lines, molecular clustering research, and experimental validation all point to the role of PANoptosis in cancer and highlight its potential as a target for therapeutic intervention. ZBP1-mediated PANoptosis is how IFN-γ and KPT-330 prevent the growth of tumors in animal models of melanoma and colorectal cancer [108]. The apoptosis-related molecule CASP2 significantly inhibits the proliferation, invasion, and migration capabilities of hepatocellular carcinoma (HCC) cells [109]. Caspase-8, a key molecule regulated by PANoptosis, displays contrasting expression across various malignancies. In certain cases, such as small cell lung cancer, renal cell carcinoma, and prostate cancer, its expression levels are relatively low. Conversely, in entities such as glioblastoma, cervical cancer, pancreatic cancer, and liver cancer, caspase-8 activity is increased [110, 111]. Researchers have divided 67 prostate cancer tissues into different stages of tumor progression and measured RNA expression and tumor growth, among other factors. RIPK3 expression is elevated in early-stage prostate cancer but significantly decreases in late-stage cancer [112]. This finding suggests that necrotic mutations are initiated during tumor onset, whereas cancer cells withstand them as the disease progresses. Cyclin-dependent kinase-1 (CDK1) is significantly associated

with poor clinical outcomes in adrenocortical carcinoma (ACC). Important PANoptosis molecules, such as Zbp1, caspase-8, and Gsdmd, are strongly positively correlated with prognosis in patients with melanoma and their likelihood of survival. By turning on ZBP1, researchers were able to successfully induce PANoptosis in melanoma cells, confirming the therapeutic impact of PANoptosis [68]. The formation of adrenocortical carcinoma (ACC) involves ZBP1-mediated PANoptosis, which is regulated by CDK1. Resveratrol, a CDK1 inhibitor, has been reported to have preventive effects on eliminating malignancies [113].

Detection methods for PANoptosis

(1) Observation of cell morphology revealed condensed chromatin, fragmented DNA, shrinking cells, compromised membranes, and apoptotic body generation.
(2) Detection of key proteins related to different RCDs: Molecular markersw including pyroptosis-related proteins (e.g., CASP1, GSDMD, gasdermin E [GSDME], AIM2, MEFV, and NLRP3), apoptosis-related proteins (e.g., CASP8, CASP3, CASP7, BCL2, and BCL2-associated X apoptosis regulator [BAX]), and necroptosis-related proteins (p-/t-MLKL, p-/t-RIPK1, p-/t-RIPK3, and ZBP1), were detected via real-time PCR and/or western blotting. One to three indicators of each PCD type can be selected, but indicators for all three types must be included.
(3) Cell death detection: Cell survival was evaluated with the Cell Counting Kit-8/MTT protocol. Various cell death mechanisms were detected through annexin V-FITC/PI flow cytometry, where Annexin V-only positive cells indicate early apoptosis, and dual positivity signifies late apoptosis or pyroptosis. Additional assessment includes Y-PRO-1/PI staining, where PI + cells represent necrosis and YP1 + cells indicate either apoptosis or necrosis.
(4) Other indicator detection methods include Annexin V-FITC and PI costaining, terminal deoxynucleotidyl transferase dUTP nick end labeling, JC-1 staining, ELISA detection of inflammatory factor release, immunoblotting, flow cytometry, and other techniques to detect the expression of the NLRP3 inflammasome and CASP1 activation (Table 3).

Table 3 Summary of the detection methods for PANoptosis

Related metabolic processes	Detection Indicator	
Cell morphology	Cytoplasmic swelling and membrane rupture	
	Chromatin condensation DNA fragmentation	
	Cell membrane blebbing	
	Formation of apoptotic bodies	
Metabolic index	Pyroptosis related	Caspase-1
		Caspase-4
		GSDMD
	Apoptosis related	Caspase-3
		Caspase-7
		Caspase-8
	Necrosis related	MLKL
		RIPK1
		RIPK3
Detection of cell death type	Early apoptotic cells	Annexin V-FITC/PI flow cytometry Annexin V result is single positive staining
	Late-stage apoptotic or pyroptotic cells	Annexin V-FITC/PI flow cytometry results are double positive staining
	Necrotic cells	Y-PRO-1/PI staining result is PI positive
	Apoptosis and necrosis	Y-PRO-1/PI staining result is positive for YP1

Relationships among cuproptosis, ferroptosis, PANoptosis, and the immune microenvironment

Cell regulatory and inhibitory networks in the TME promote tumor development and progression through metabolic reprogramming and hypoxia regulation. The main components of the TME include immune cells, mesenchymal cells, endothelial cells, and the extracellular matrix [114, 115]. Immune, mesenchymal, and endothelial cells can secrete various cytokines that directly act on tumor cells, such as TNF and transforming growth factor (TGF)-β. These cytokines regulate each other and jointly form a network of inhibitory immune molecules, allowing tumor cells to evade the body's immune system and achieve immune escape [116]. Studies have shown that RCD, including cuproptosis, ferroptosis, and PANoptosis, is closely related to the TME. RCD can regulate the malignant process of tumors by directly or indirectly affecting the reprogramming of the TME (Fig. 5).

Relationship between cuproptosis and the immune microenvironment

Studies have shown that the Cu content in the serum and tissues of patients with various tumor types is significantly higher than that in the normal population and is related to tumor stage or progression [29]. Increased Cu content can promote the proliferation and metastasis of tumor cells and angiogenesis [117]. It is currently believed that cuproptosis is related to immune cell infiltration and plays a specific role in shaping the antitumor immune environment.

Increased expression of PD-L1 serves as a self-defense strategy employed by cancer cells to evade the antitumor activity of the immune system [118]. Tumor cell surface PD-L1 expression is significantly correlated with that on T lymphocytes, and this interaction with the PDCD1/

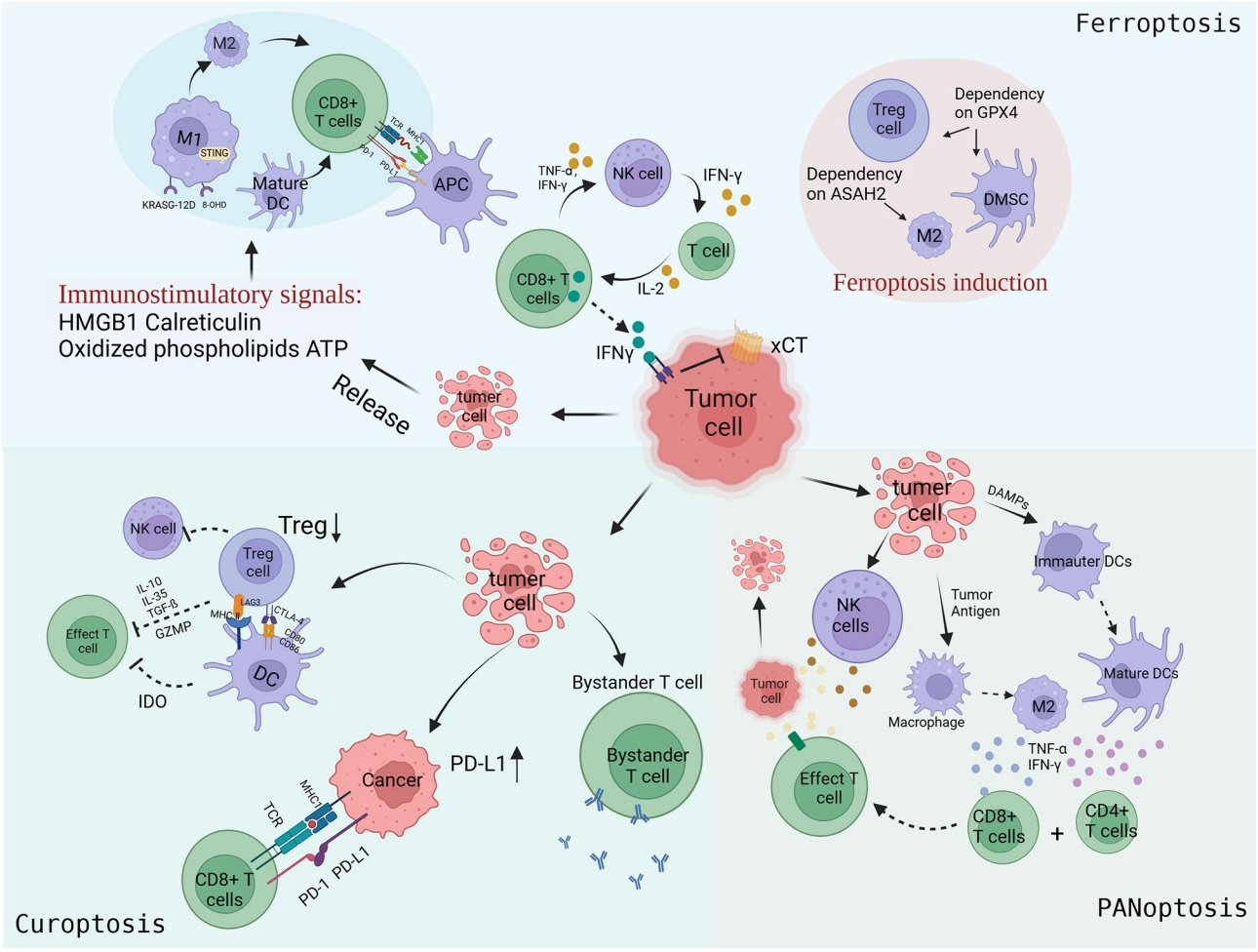

Fig. 5 Summary of novel RCD patterns affecting the TME in tumor cells. The effects of tumor cell ferroptosis, cuproptosis, and necroptosis on immune cells in the TME are summarized

PD-1 receptor on cells hampers the cytotoxic effects of T cells against tumors, resulting in immune evasion [119]. Recent investigations revealed that cellular copper concentrations play a significant role in regulating PD-L1 expression in cancer cells, enabling them to evade immune surveillance. Notably, increased copper increases PD-L1 expression at both the transcriptional and protein levels in malignancies.In the majority of cancer varieties, CTR1 shows a strong correlation with PD-L1, unlike in corresponding healthy tissues. Elevated CTR1 levels in neuroblastoma cells lead to an excess of copper, enhancing the STAT and EGFR signaling routes, consequently boosting the quantity of PD-L1. Conversely, cancerous tissues are abundant in copper ions, and the presence of copper chelators can efficiently eliminate these ions, leading to their anticancer properties. Copper binding agents like dextran-catechin, thieno[3,2-c] pyridine (JYFY-001), and TEPA reduce the phosphorylation of STAT3 and EGFR through the suppression of the JAK/STAT pathway, suppression of PD-L1 expression, initiation of PD-L1 ubiquitination and breakdown, augmentation of tumor-penetrating clusters of distinct CD^{8+} T and NK cells, and deceleration of tumor progression [120]. In a variety of relevant cancer models, copper apoptosis and immune correlation analyses revealed that the number of proinflammatory cells (including $CD8^+$ T cells) in the low-risk group was significantly greater than that in the high-risk group and that the expression of immune checkpoint genes (including PD-1 and CTLA-4) was increased [121–123]. Therefore, copper-induced apoptosis may regulate the expression of immune checkpoint proteins, thereby affecting the immune escape mechanism of tumors.

A comprehensive pancancer analysis revealed an association between SLC31A1 expression and the presence of $CD8^+$ T cells, $CD4^+$ T lymphocytes, and macrophages within the tumor microenvironment (TME) [124]. SLC31A1 expression is negatively correlated with the infiltration of plasmacytoid dendritic cells (DCs), natural killer (NK) cells, and $CD8^+$ T cells in gliomas and is

positively correlated with a high abundance of immunosuppressive immune cell types [125]. In most tumors, the occurrence of cuproptosis is significantly inversely correlated with the expression of TNF receptor superfamily members 14 (TNFRSF14) and 25 (TNFRSF25) [126]. Low TNFRSF14 expression is associated with poor prognosis in patients with bladder cancer [127].

Zhang et al. [128] reported that reduced chromodomain helicase DNA binding protein 7 (CHD7/CRG) levels in HCC patients were correlated with increased levels of protumor immune elements within tumors, although the number of antitumor immune cells remained stable [128]. Investigations have revealed that varying expression levels of cuproptosis-related genes within bladder tumors significantly influence the tumor microenvironment [129]. Breast cancer tumors with increased SLC31A1 expression exhibit increased infiltration by immune cells such as $CD4^+$T cells, macrophages, neutrophils, and dendritic cells. The increased expression of immune checkpoint proteins such as PD-L1 and CTLA4 further implies potential detrimental effects on patient prognosis [130]. In patients with endometrial and hepatocellular carcinoma, tumor FDX1 expression is positively correlated with $CD8^+$T-cell infiltration and negatively correlated with the expression of immunosuppressive molecules, suggesting that FDX1-dependent copper modulation may potentiate antitumor immune responses [131, 132].

The relationship between ferroptosis and the immune microenvironment

The link between ferroptosis and the TME is intricate. Ferroptosis in cancerous cells could potentially activate or adjust immune reactions within the TME. Conversely, the vulnerability of immune cells in the TME to ferroptosis differs significantly, with various immune cell types capable of either amplifying or suppressing ferroptosis in cancerous cells. Consequently, the following section delves into how ferroptosis interacts with the immune microenvironment of tumors.

Within the intricate workings of the tumor microenvironment (TME), immune cells, particularly $CD8^+$T cells, are crucial in controlling the ferroptosis of cancer cells. The generation of IFNγ by $CD8^+$T cells, stimulated through immunotherapy, exerts twofold impacts on the ferroptosis of cancer cells. IFNγ, on one side, suppresses system Xc- (SLC3A2 and SLC7A11), hinders the absorption of cystine by tumor cells, and prevents tumor cell GSH from detoxifying lipid peroxides, thus making tumors more susceptible to ferroptosis [39]. Conversely, IFNγ enhances the expression of ACSL4 and aids in the ACSL4-driven creation of PUFA-PLs, particularly those with arachidonic acid, thus boosting the integration of arachidonic acid into acyl chain phospholipids, facilitating lipid peroxidation, and triggering ferroptosis in cancerous cells [133, 134]. Significantly, the presence of IFNγ from $CD8^+$T cells and arachidonic acid in the TME is recognized as a fundamental factor in triggering cancer cell ferroptosis. Furthermore, $CD8^+$T cells have the ability to obstruct the Xc- system via IFNγ, leading to a decrease in cystine and GSH production, which in turn diminishes the creation of GSH–platinum complexes, elevates intracellular platinum levels, and heightens the susceptibility of cancer cells to cisplatin-based chemotherapy [135].Regarding T cells, numerous research works have demonstrated their comparative resistance to ferroptosis across different models. As an illustration, numerous methods involving nanoparticles to trigger ferroptosis pose no harm to T cells and also enhance their penetration into the TME [136–138]. However, some studies have shown that T cells are susceptible to ferroptosis induced by GPX4 inhibition. T cells lacking GPX4 (derived from mice with T-cell-specific Gpx4 deletion) rapidly accumulate lipid peroxides in their cell membranes and eventually succumb to ferroptosis [139]. A lack of $CD8^+$T-cell ASCL4 could offer protection against ferroptosis while diminishing its cancer-fighting properties [140]. Possibly owing to the varying sensitivities of $CD8^+$T cells and cancer cells towards ferroptosis, certain academics theorize that inhibitors of ferroptosis could boost $CD8^+$T cells' capacity to withstand ferroptosis, offering a hopeful approach to enhance immunotherapy [134].

The ferroptosis of tumor cells can regulate macrophage polarization. Ferroptosis effectively increases the number of macrophages through the polarization of macrophages and the upregulation of PD-L1 [141–145]. TAMs show strong plasticity and can differentiate into an immunostimulatory M1 phenotype or an immunosuppressive M2 phenotype.In-depth research in cancer immunology is focused on eliminating M2 TAMs or transforming them into a more cancer-fighting M1 phenotype. M2-like TAMs, in contrast to protumor M1-like TAMs, exhibit greater sensitivity to ferroptosis induced by GPX4 [146, 147]. Elevated levels of ferritin heavy chain 1 in M1 macrophages enhance the creation of ferritin and the capture of iron within cells, while diminished ferroportin levels aid in cell resistance to ferroptosis [148]. Furthermore, M2-like TAMs are distinguished by their inherent ability to suppress the immune system and are devoid of NOS2/iNOS-driven nitric oxide production, which impedes the removal of lipid peroxides. Encouraging the ferroptosis of M2-like TAMs, excluding M1-like TAMs, shows potential as a strategy to combat the immunosuppressive TME and improve cancer immunotherapy effectiveness [146]. A different research emphasized the vital function of the TYRO3 tyrosine protein kinase receptor in controlling ferroptosis within the TME [149]. It was discovered

that TYRO3 suppresses ferroptosis in cancerous cells and lowers the M1/M2 macrophage ratio, fostering a tumor-enhancing tumor microenvironment (TME). In contrast, inhibiting TYRO3 leads to tumor ferroptosis and changes the M1/M2 macrophage ratio, thereby heightening tumor responsiveness to anti-programmed cell death protein 1 (PD-1) treatment.

NK cells play a central role in antitumor immunity. NK cell dysfunction in the TME has been associated with oxidative stress driven by lipid peroxidation; activation of the NRF2 transcription factor has been shown to rescue NK cell function and antitumor activity [150, 151].Aligning with these results, blocking ferroptosis enhanced the survival of NK cells in tumors.

In the context of ferroptosis, Regulatory T cells (Tregs) constitute a group of $CD4^+$ T cells known for their immunosuppressive function in cancer [152]. The absence of GPX4 triggers lipid peroxidation and ferroptosis in Treg cells post T-cell receptor signaling, enhancing the production of interleukin-1β (IL-1β), which in turn stimulates T helper 17 (TH17) responses. The results indicate that Tregs lacking GPX4 inhibit the proliferation of tumors and bolster the body's defense against them [153]. The link between Tregs and ferroptosis remains inadequately explained, presenting difficulties in comprehending how immune cells respond to ferroptosis.

Fibroblasts linked to cancer, known as CAFs, play a crucial role in the TME, significantly influencing both innate and adaptive immune responses [154]. CAFs play a role in inhibiting ferroptosis in cancer cells by upregulating the long noncoding RNA DLEU1 or secreting the microRNA miR-522 [155].

Dendritic cells (DCs) stand as the strongest antigen-presenting cells essential for activating naive T-cells and facilitating T-cell-dependent immune responses [156]. Both the GPX4 inhibitor RSL3 and the lipid peroxidation byproduct 4-hydroxynonenal (4-HNE) might lead to DC malfunction [157].The interaction between ferroptotic cancer cells and DCs might vary based on the ferroptosis phase. During the initial phase of ferroptosis, cancer cells initiate the maturation of DCs; yet, as ferroptosis progresses, their capacity to facilitate DC maturation diminishes, yet these advanced ferroptotic cells remain capable of being efficiently phagocytosed by DCs [158].

The presence of tumor ferroptosis plays a role in the immune response and immune treatment of cancer. Ferroptosis represents a type of immunogenic cell death (ICD), exhibiting certain characteristics of ICD [158]. Certain compounds emitted by ICD cells, like calreticulin (CRT) and high-mobility group box 1 (HMGB1), might engage with phagocytic and purinergic receptors in immune cells, subsequently triggering cytotoxic T lymphocyte (CTL)-induced immune reactions and adaptive immunity [159]. In human glioblastoma, ferroptosis is associated with necrosis and predicts poor survival [160]. Ferroptosis may cause brain tumor necrosis and have a protumorigenic effect. However, the crosstalk between ferroptosis, necrosis, and apoptosis pathways and how this affects the immune response to tumors are still unclear. How ferroptotic cells are cleared by phagocytes is also poorly understood.

The relationship between PANoptosis and the immune microenvironment

PANoptosis may stimulate the tumor microenvironment (TME) to achieve antitumor effects [161, 162]. Specifically, traditional apoptosis is usually reduced in the tumor microenvironment (TME). Although it lacks immunogenicity, mitochondrial outer membrane permeabilization can trigger caspase-independent cell death in the absence of caspases, which can activate antitumor immunity and significantly enhance antitumor activity, as has been validated in the mouse rectal cancer CT26 [143, 144, 163, 164]. Necroptosis can facilitate dendritic cell maturation and significantly increase the antitumor potential of $CD8^+$ T cells [165, 166]. Necroptosis, an immunostimulatory mode of programmed cell death, actively facilitates immune cell infiltration within the tumor microenvironment (TME) via the release of inflammatory cytokines, thus contributing to antitumor immunity. Under normal conditions, excessive ZBP1-mediated cell death and inflammation can be detrimental, but ZBP1 has a supportive function during cancer development. The cascade of necroptotic signals mediated by ZBP1 leads to the release of mtDNA, which subsequently triggers an IFN-I response via the cGAS–STING pathway, forming a robust antitumor immune positive feedback loop [167, 168]. This process more effectively activates the NF-κB and IFN-I signaling pathways, enhancing the cytotoxicity of $CD8^+$ T lymphocytes (CTLs) against immunogenic tumor-associated antigens and promoting $CD4^+$ Th1 responses, resulting in more durable and stronger resistance to B16 melanoma [169]. PANoptosis features enhance immune infiltration in tumors, promoting antitumor immunity. In addition to the infiltration of effector T cells, activated T cells, and other antitumor immune cells, there is also an increase in the infiltration of Treg cells. Treg cells can inhibit the proliferation of effector T cells, secrete cytokines, and participate in immune evasion in certain tumors. PANoptosis may exhibit characteristics of immunogenic cell death, producing proinflammatory cytokines such as IL-1B and IL-18 to facilitate immune cell infiltration into the tumor microenvironment (TME) [170]. Upon encountering diverse antigens, T cells initiate their response by releasing distinctive signaling molecules such as IFN-γ. This triggers PANoptosis, which involves immune responses and tumor clearance during the PANoptosis process [87]. Like

other specific immune cells, which release TNF-α and IFN-γ via their effector functions [171], NK cells execute direct cancer cell death via perforin and granzyme release and via multiple mechanisms, such as PANoptosis [172]. Natural killer (NK) cells are part of the innate immune system and are classic tumor-killing cells that can secrete cytokines and regulate the body's immune response and angiogenesis. NK cells can recognize and selectively kill tumor cells through surface receptors. They may create a favorable microenvironment for antigen-specific T-cell immune responses, activate other immune cells, enhance the effect of combined immune responses, and improve the effectiveness of tumor destruction [173]. In addition to killing cancer cells by secreting perforins and granzymes, NK cells can also directly kill cancer cells through a variety of mechanisms, including PANoptosis [172]. In the constructed liver cancer PANoptosis-related gene model, the quantification of tumor-infiltrating immune cells revealed that the abundance of NK cells in the high-PAN score group was significantly greater than that in the low-PAN score group in the TME [174]. The PANoptosis-related gene RING Finger protein 34 (RNF34) was positively correlated with CD56dim NK cells. Although these observations are rare, they emphasize the involvement of NK cells in PANoptosis. Dendritic cells, as key antigen-presenting cells, simultaneously produce cytokines to trigger a programmed cell death response, PANoptosis, during the delivery of cancer antigens to T cells [171, 175]. After assessing immune cell infiltration in 33 cancer types, researchers reported that the PAN score was significantly negatively correlated with M1-like macrophages and positively correlated with M2-like macrophages [176]. These findings imply that macrophages play a pivotal role in the TME response and potentially govern the immunological milieu of tumors through their control of PANoptosis. DCs function to phagocytose dead cells and interact with the TME in a complex manner via a PANoptosis mechanism. During extensive tumor cell apoptosis, dendritic cells discern specific signaling molecules, engulfing apoptotic cells that bear these signals. These engulfed cells then present tumor antigens, triggering immune activation, particularly of T cells and B cells, thereby regulating immune responses against tumors. Successful antitumor immunity relies on distinct DC subsets within the tumor microenvironment, along with cytokine (IFN-γ)-mediated communication between DCs and T cells, increasing $CD8^+$ T-cell-driven tumor destruction [177].

Like other regulated cell death pathways, PANoptosis can be harnessed to induce highly immunogenic tumors. Research has shown that immunogenic PANoptotic cell death can reprogram an immunosuppressive environment and increase innate immune responses by promoting dendritic cell (DC) maturation and macrophage polarization through the release of damage-associated molecular patterns (DAMPs) [178]. The combined effects of cytokines such as TNF-α and IFN-γ produced by immune cells can trigger inflammatory cell death, leading to immunogenic cell death in cancer cells. Targeting PANoptotic cell death not only helps to counteract immune evasion but also provides a feedback loop for immune activation, which is crucial for overcoming resistance in refractory cancers. PANoptosis enhances tumor-specific immunity and is positively associated with the infiltration of immune cells such as $CD4^+$ T cells, $CD8^+$ T cells, and NK cells within the tumor microenvironment (TME). Immune checkpoint molecules, including CCL2, CD274, CD4, CXCR4, and LAG3, are positively correlated with PANoptotic characteristics [170]. Thus, PANoptosis plays a significant role in tumor immunity by promoting immune cell infiltration, increasing the expression of immune checkpoint regulators, and enhancing tumor immunogenicity. Further investigations into the relationships between these immune variables and PANoptosis may provide new strategies to improve cancer therapy. The interplay between immune components and PANoptosis holds promising therapeutic and prognostic potential in cancer treatment.

Nanoengineering strategies targeting cuproptosis, ferroptosis, and PANoptosis

Cuproptosis

Qiao et al. [179] prepared copper-quinone-glucose oxidase (GOx) (CQG) nanoparticles (NPs) with four excellent mimicking enzyme activities and combined them with starvation therapy to induce cuproptosis and pyroptosis, resulting in increased immunotherapy effects (Fig. 6). CQG NPs generate substantial amounts of oxygen to suppress hypoxia-inducible factor 1 subunit alpha (HIF1A/HIF1α) and deplete GSH, disrupting the antioxidant defense of tumor cells by inhibiting the expression of nuclear factor E2-related factor 2 (NRF2) and NAD(P)H quinone dehydrogenase 1 (NQO1). The CQG NPs also promoted the conversion of endogenous $O_2^{\bullet-}$, producing abundant H_2O_2. Under the costimulation of a mildly acidic TME, H_2O_2 generates highly toxic OH^-. The coordinated cuproptosis and pyroptosis mediated by CQG NPs can effectively convert M2 macrophages into the M1 phenotype, promote DC maturation, and activate strong host immunity. The Cu released by the self-destruction of the CQG NPs significantly facilitated cuproptosis.

Zhang et al. [180] prepared an RNA interference therapy based on a biomimetic nanodelivery system (TPM-Cu-MOF/siATP7a) for brain metastasis therapy that specifically blocks Cu transporters and induces cuproptosis. Both in vitro and in vivo experiments revealed that TP-M-Cu-MOF/siATP7a improved the therapeutic effect in small cell lung cancer brain metastasis-bearing

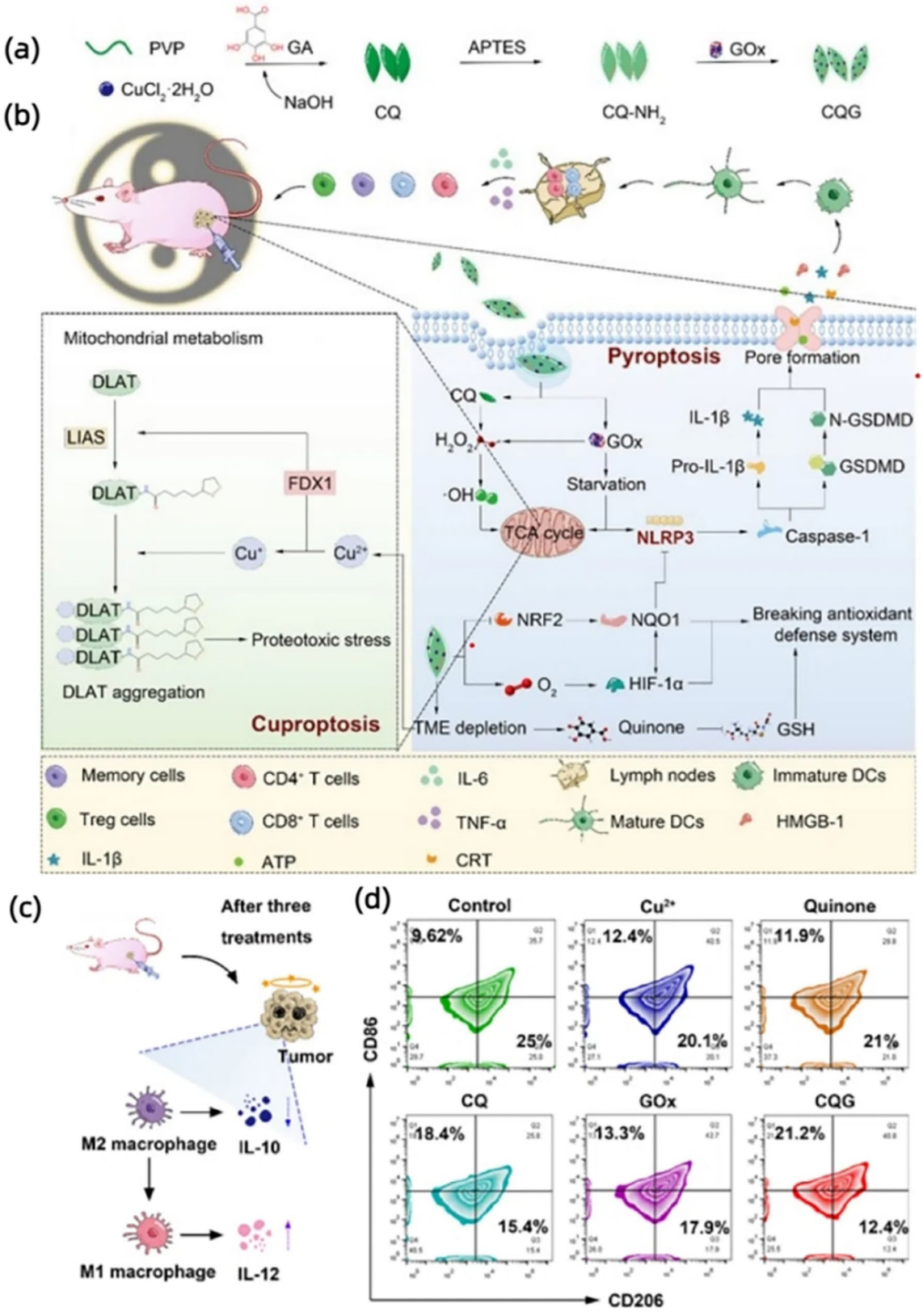

Fig. 6 (**a**) Schematic of CQG NP synthesis. (**b**) Anticancer mechanism of the synergistic activation of immunity by CQG-induced pyroptosis and cuproptosis. (**c**) Schematic of macrophage polarization and the secretion of associated cytokines in vivo. (**d**) Representative flow cytometry plots and the corresponding quantification of (**c**) M2-type macrophages ($CD86^-CD206^+$) [179]

mice and exhibited negligible systemic toxicity, targeting Cu-dependent cellular processes and ionophore metals. Complementary treatment combinations offer alternative strategies with great potential for treating tumor metastasis.

Guo et al. [181] developed an amphiphilic, biodegradable polymer, PHPM (2-hydroxy-3-phenoxypropyl methacrylate), distinguished by its ROS-responsive thioketal linkages within the backbone and complementary side chains containing carboxylic acids. ES and Cu were encapsulated in PHPM to form NP@ESCu. NP@ESCu was thought to selectively accumulate at the tumor site in mice with bladder cancer and then to be efficiently taken up by cancer cells. The excess ROS in tumor cells subsequently triggered rapid cleavage of the thioketal bond in PHPM, leading to polymer degradation, NP dissociation, and, ultimately, the release of the encapsulated ES and Cu. Notably, the consecutive increase in copper content enhances PD-L1 surface expression on cancer cells, thereby increasing the antitumor potency of αPD-L1. NP@ESCu intervention effectively matures dendritic cells, stimulates $CD8^+$ T-cell infiltration within tumors, and prompts M2-like TAMs to convert into the proinflammatory M1 phenotype, inhibiting the accumulation of myeloid-derived suppressor cells. Additionally, NP@ESCu effectively reprogrammed the immunosuppressive tumor microenvironment through cuproptosis, thereby eliciting robust antitumor immunity in bladder cancer mouse models. This innovative strategy, which combines copper dUTP with PD-L1, holds great promise for treating "cold" immune tumors in prostate cancer patients in future clinical applications.

Qi et al. [182]. prepared Cu_3P nanoparticles with photothermal and photodynamic properties, which can accumulate at the tumor site under near-infrared laser irradiation and effectively inhibit tumor growth. Studies have shown that Cu phosphide (Cu_3P) NPs can induce *HSP70* and *HO-1* expression, increase intracellular ROS levels, accelerate cell death, and inhibit tumor growth. Under acidic TME conditions and the effects of a nanoscale drug delivery platform composed of zinc oxide and Cu sulfate NPs, doxorubicin, and pirfenidone, ROS were continuously generated through cascade reactions, depleting GSH and regulating the intracellular redox environment. Deng et al [183]. Developed a nanoplatform based on ZnO@cus for chemotherapy and photothermal combination therapy for tumor.The nanoplatform has dual pH-sensitive properties that can be specifically triggered in the TME and in tumor cells. Mechanistic studies revealed that Z@C-D/P+laser treatment modulated the intracellular redox environment by promoting ROS production and reducing GSH and GPX4 levels. The highly efficient Z@C-D/P could be a promising nanoplatform for the treatment of breast cancer metastasis.

Ferroptosis

Fe ions, via the Fenton reaction, generate harmful hydroxyl radicals, and their accumulation potentially triggers ferroptotic cell death [184]. The pivotal role of iron ions and hydrogen peroxide in cellular reactions is emphasized, as various bionanomaterials, such as Fe ions and H2O2, which specifically target ferroptosis in malignant cells, have been strategically developed to increase the concentration of Fenton reactants. Wan et al. [185] constructed an Fe-based metal–organic framework (MOF), which was skillfully coated with a cancer cell membrane and decorated with GOx, functioning as a sophisticated nanotherapeutic agent. Upon reaching the tumor microenvironment, its efficient interaction with the abundant glutathione (GSH) leads to disintegration of the MOF structure, subsequently releasing Fe^{2+} ions via redox reactions involving Fe^{3+}. GOx can catalyze the conversion of glucose to H_2O_2, promote the Fenton reaction, and accelerate OH^- production. Nanotherapeutics that inhibit GPX4 activity have also been used to induce ferroptosis. The primary approach involves dual tactics: first, nanodrugs with direct GPX4 suppression are administered to target cancer cells; second, GPX4 activity is indirectly hindered by effectively depleting GSH or obstructing its biosynthetic route [186].

Zuo et al. [187] designed and synthesized a novel nanoformulation, FPBC@SN NPs, which release ferritin, sorafenib (SRF), and an indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor (NLG919) under acidic conditions. NLG919, through its mechanism of IDO1 inhibition and tryptophan metabolism suppression, actively aids in stimulating antitumor immunity. Notably, SRF has been employed in certain clinical trials as a chemotherapy agent, achieving this effect by impairing glutathione synthesis and downregulating GPX4 activity. System Xc- serves as a vital antioxidant in cellular processes [188]. Its ability to suppress ferroptosis in malignancies has gained traction as a promising therapeutic approach. Some inhibitors, such as erastin, sulfasalazine (SSZ), and SRF, have been employed in the fight against cancer. Xin et al. [189] successfully synthesized an SSZ-Fe^{2+}@DSSD nanomedicine. High GSH levels disrupt disulfide bonds in this system, releasing SSZ and Fe^{2+}. SSZ exerts its ferroptosis-inducing effect by concurrently suppressing the functionality of system Xc–, and Fe^{2+} facilitates the catalytic process of the Fenton reaction.

The extensive presence of PUFAs significantly influences lipid peroxidation within cells. A potential strategy could be the use of nanomaterials to introduce external lipid peroxides, thereby promoting ferroptosis. Zheng et al. [190] covalently combined the polyethylenimine/TP53 plasmid complex with Fe^{3+}, Fe^{2+}, and polyphenolic tannic acid to form a metal–organic network (MON–TP53) NPs, which both inhibits SLC7A11 and mediates the

Fenton reaction to increase the level of ROS, promoting ferroptosis in HT1080 cells. Shen et al. [191] synthesized FeGd-HN@Pt@LF/RGD2-cDDP conjugates from Fe_3O_4/Gd_2O_3 hybrid NPs, lactoferrin (LF), and cisplatin (cDDP). When internalized into U87 cells, Fe ions and cDDP were released during endosome uptake and degradation, accelerating the Fenton reaction to produce ROS and induce ferroptosis. Liu et al. [192] presented a streamlined solvent-free strategy for the synthesis of ultrathin manganese-based layered double hydroxide nanosheets, which showed exceptional sensitivity to the proinflammatory cytokine IFN-γ (denoted as IFN-γ/uMn-LDH). These nanosheets exhibited a synergistic effect in promoting ferroptosis and boosting systemic immunity. This innovative technique offers a promising solution for the harmonious regulation of these processes, potentially resolving existing challenges in cancer immunotherapy, as depicted in Fig. 7.

PANoptosis

Zhou et al. [178] designed an immune-reediting antitumor NP (PFH@Lipo-PpIX@EV) based on the PANoptotic pathway promoted by engineered extracellular vesicles (EVs). NPs are nanovesicle-sensitive, ultrasound-controlled, immune-engineered therapies for tumors. NPs have sonosensitive activity and a protein transport function, which can effectively overcome the resistance of refractory tumors to immunotherapy by leveraging the cancer immune cycle (Fig. 8). PFH@Lipo-PpIX@EV could perform chemical, physical, and biological catalysis and induce a nonredundant and highly immunogenic PANoptotic cell death pathway. This treatment regimen demonstrated potent distant tumor suppression and effective resistance to tumor lung metastasis and rechallenge in a triple-negative breast cancer mouse tumor model.

Song et al. [193] developed a novel nanocarrier, folic acid-cholesterol-sodium alginate (FCA), for the concurrent delivery of metformin (MET) and doxorubicin (DOX) to xenograft melanoma tumors. This advanced nanosystem efficiently induced a combined cell death response, known as PANoptosis, involving pyroptosis, apoptosis, and necroptosis. This dual-drug approach not only impeded melanoma progression but also significantly increased antitumor efficacy. In-depth investigations revealed that carbon NP-encapsulated MET and DOX within FCA NPs triggered PANoptosis both in cellular cultures and in living organisms, thereby enhancing antimelanoma effects at the mechanistic level.

In cancer immunotherapy, nanomaterials are employed to deliver drugs, genes, or immunomodulators, thereby enhancing the ability of the immune system to combat cancer. While nanotherapy offers numerous benefits in this context, it also presents substantial challenges. On the positive side, nanocarriers can be engineered to specifically target tumor cells or immune cells within the tumor microenvironment, minimizing drug toxicity to normal tissues and increasing treatment precision. Additionally, nanoparticles can shield drugs from degradation, improving their stability and extending their half-life. This targeted approach enhances drug permeability at tumor sites and improves therapeutic outcomes. However, the development and production of nanoparticles are complex and costly, with challenges in achieving uniform size and consistency. Large-scale manufacturing and standardization remain important hurdles. Moreover, tumor heterogeneity, such as varying genetic mutations and immune escape mechanisms, can hinder the effectiveness of nanotherapy across all cancer cells, leading to inconsistent treatment results. The biodistribution and clearance of nanoparticles in the body are also difficult to control, as some may be rapidly cleared by nontarget organs such as the liver and spleen, reducing their accumulation at the tumor site and thus diminishing therapeutic efficacy.

Conclusions and perspectives

Cell death is one of the links in metabolism. Like cell proliferation and differentiation, normal cell death is important for ensuring the normal function of cells and organ metabolism. Since Keer et al. discovered apoptosis, the first described form of cell death, in 1972, scientists have discovered more than ten forms of cell death. Ferroptosis, cuproptosis, and PANoptosis are regulatory forms of cell death discovered in recent years (Table 4). Compared with traditional forms of cell death, immune microenvironment reprogramming has attracted more attention. Tumor, immune, stromal, and other cells in the TME coexist and engage in complex interactions, significantly affecting tumor growth and progression. Ferroptosis, cuproptosis, PANoptosis, and the TME are linked in complex ways. While ferroptosis, cuproptosis, and PANoptosis in tumor cells may trigger or regulate the immune response in the TME, the sensitivity of immune cells in the TME to these new forms of cell death varies significantly. In addition, different forms of immune cell death can regulate the proliferation and death of tumor cells through direct or indirect effects.

Recent studies have revealed a synergistic effect of $CD8^+$T cells and fatty acids in instigating ferroptosis within tumor cells. Notably, the secretion of IFN-γ from $CD8^+$T cells contributes to ferroptosis, yet standalone IFN-γ is insufficient for triggering this cell death mechanism. Fatty acids are another type of molecule that can sensitize tumor cells to ferroptosis. Combining both approaches can more effectively promote ferroptosis in cancer cells [194]. Extensive research has demonstrated the pivotal function of cuproptosis-linked genes in the

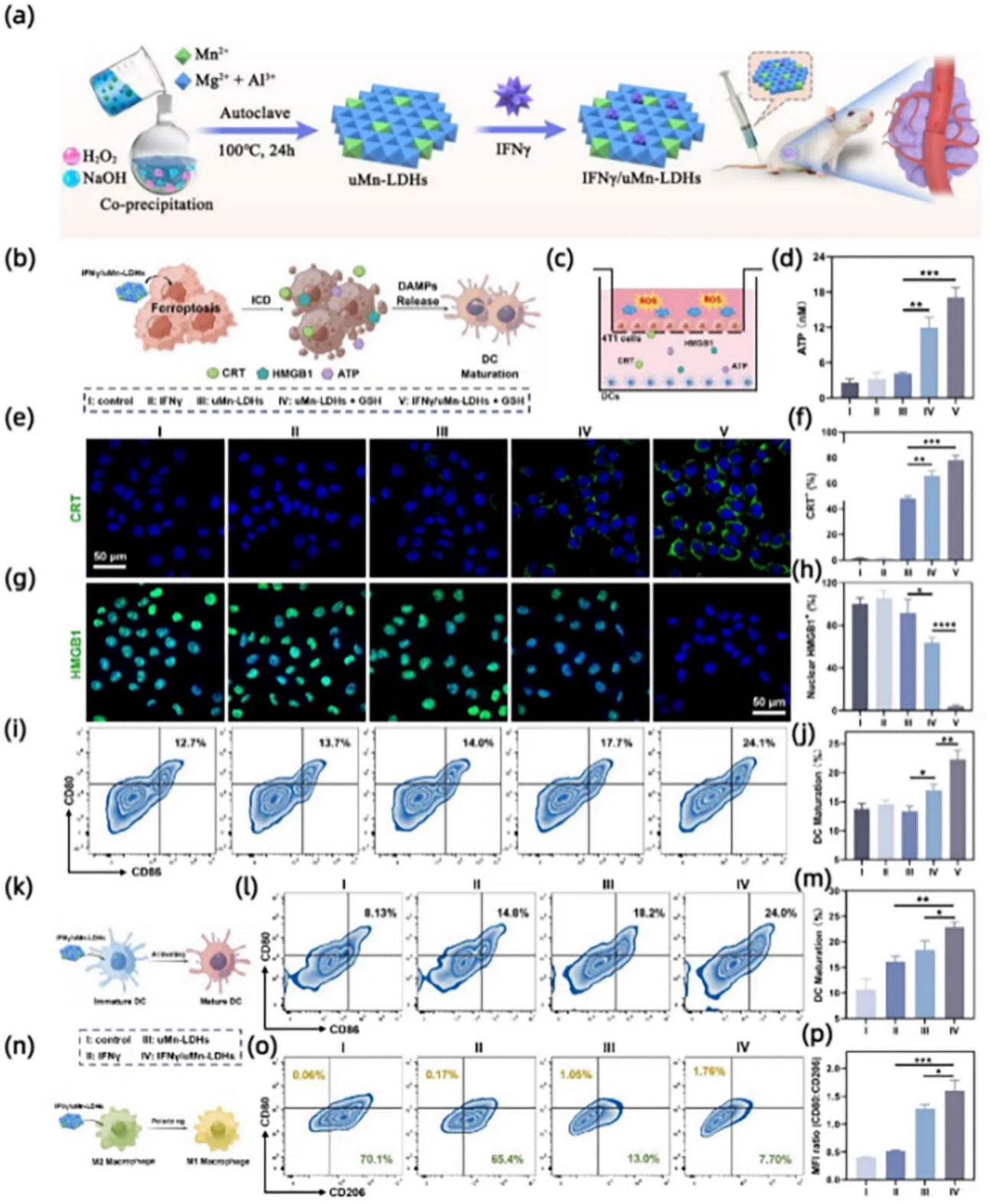

Fig. 7 (**a**) Synthesis of ultrathin Mn-based LDH nanosheets and subsequent loading of IFN-γ via electrostatic interactions. (**b**) Immune cell death induced by ferroptosis and subsequent DC maturation. (**c**-**d**) The amount of ATP released by 4T1 cells. (**e**-**f**) Quantification of 4T1 cell surface calreticulin (CRT) exposure. (**g**-**h**) Quantitative examination of HMGB1 release in cancer cell nuclei. (**i**-**j**) Quantification of bone marrow-derived DC (BMDC) maturity after 24 h of culture in different tumor cell groups. (**k**) Schematic of uMn-LDH-induced DC maturation. (**l**-**m**) Quantitative analysis of mature BMDCs incubated with various formulations. (**n**) Schematic of uMn-LDHs inducing macrophage polarization from M2 to M1. (**o**-**p**) Mean fluorescence intensity ratios of CD80 to CD206 on $CD11b^+F4/80^+$ BMDMs after the indicated treatments [192]

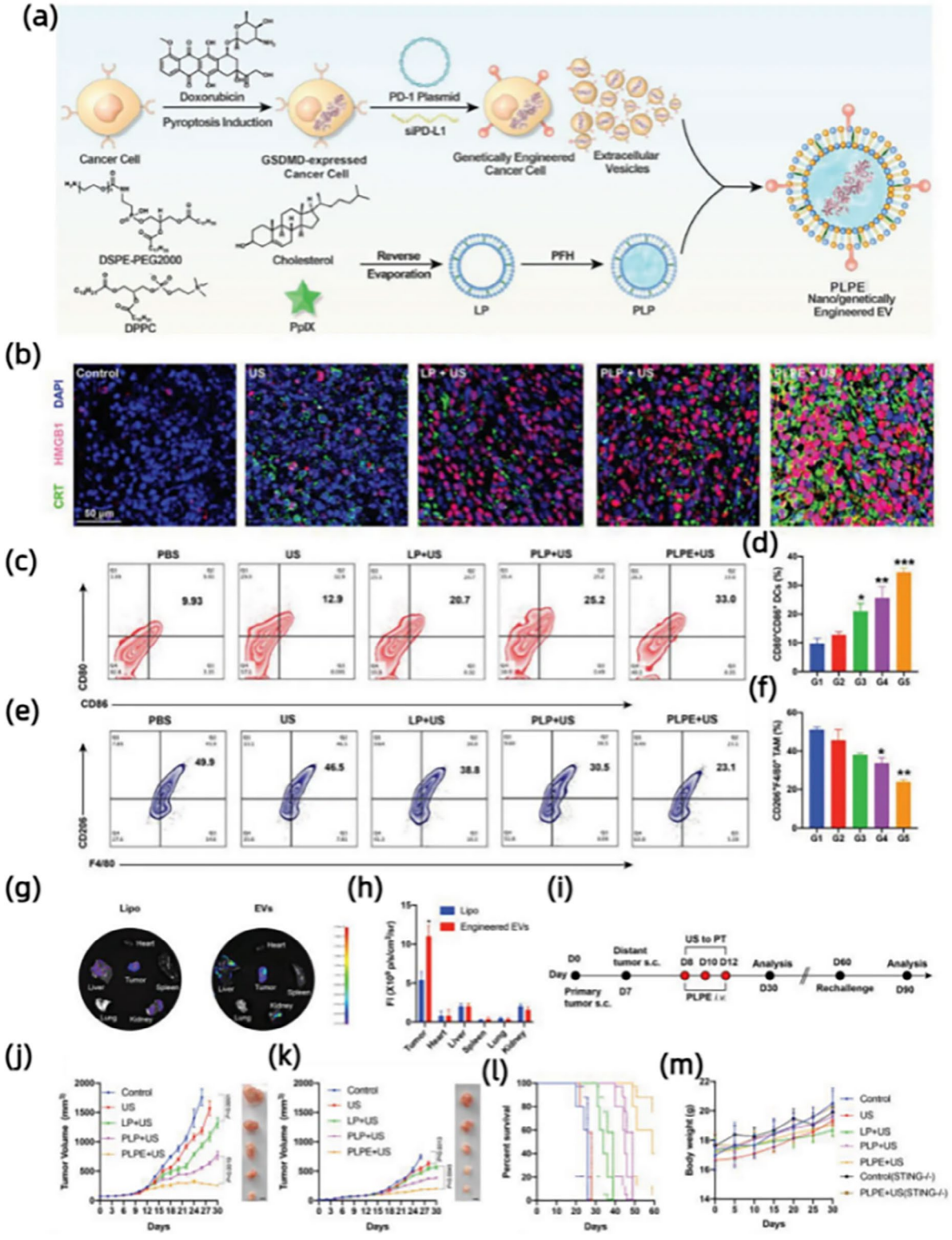

Fig. 8 (**a**) Schematic of immunogenic PANoptosis-Initiated Cancer Sono-Immune Reediting Nanotherapy. (**b**) Postdrug treatment analysis of DAMPs in 4T1 tumor tissue. (**c**–**f**) Mature DC and M2 TAM analysis and relative quantification. (**g**, **h**) Fluorescence imaging and quantitative assessment of isolated tumors and major organs 24 h after tail vein injection of Cy5.5-labeled EVs. (**i**) Experimental design to establish 4T1 primary, distant metastasis, and rechallenge models and treatment strategies. (**j**, **k**) Average tumor growth curves and corresponding representative tumor photographs of primary tumors (**j**) and distant tumors (**k**) after various treatments. (**l**) Kaplan–Meier survival curves for mice after the indicated treatments. (**m**) Changes in the weights of the mice in each group during treatment [178]

Table 4 The roles and regulatory mechanisms of cuproptosis, ferroptosis, and PANoptosis

Effector/reagent	Cell death pathways	Proposed mechanism	Cancer type	Reference
GPX4	Ferroptosis	Eliminates phospholipid hydroperoxides Wnt/beta-catenin NF2-YAP	Multiple cancers	[39, 60, 215–217]
SLC7A11	Ferroptosis	Mutations in Ecadherin–NF2–Hippo axis, SOX2-SLC7A11 regulatory axis, ATF4-SLC7A11 (xCT), FTO-SLC7A11	Multiple cancers	[39, 218]
NRF2	Ferroptosis	Activates antioxidant genes; Upregulates SLC7A11	ovarian cancer	[150]
GCH1	Ferroptosis	Involved in BH4 synthesis	colorectal cancer	[219, 220]
FSP1	Ferroptosis	Converts CoQ10 to CoQ10H2, reducing membrane phospholipid peroxidation	Multiple cancers	[221, 222]
NCOA4	Ferroptosis	NCOA4-mediated ferritinophagy	oral squamous cell carcinoma	(223)
FDX1	Cuproptosis	Fe-S cluster biosynthesis ruduce Cu(II) to Cu(I) synthesis of various steroid hormones electron transport intermediate for mitochondrial cytochromes P450	COAD	[20, 224–229)
ATP7A	Cuproptosis	ATP-driven copper ion pump	Multiple cancers	[230]
SLC31A1	Cuproptosis	High-affinity, saturable copper transporter involved in dietary copper uptake	Multiple cancers	[230–234]
DLAT	Cuproptosis	component of pyruvate dehydrogenase complex, mediate the conversion of pyruvate to acetyl-CoA	glioblastoma	[235]
LIPT1	Cuproptosis	Catalyzes the transfer of the lipoyl group from lipoyl-AMP to the specific lysine residue of lipoyl domains of lipoatedependent enzymes	ESCA	[236–238]
ADAR1	PANoptosis	ZBP1/ RIPK3	melanoma	[69]
NFS1	PANoptosis	MYC/NFS1	colorectal cancer	[239]

progression of tumors and the intricate cellular infiltration within the tumor microenvironment [195]. Therefore, targeting ferroptosis, cuproptosis, and PANoptosis are effective strategies for reprogramming the immune microenvironment and influencing the efficacy of tumor immunotherapy.

Traditional targeted therapies induce cancer cell death by interfering with specific cancer-related signaling pathways or molecular targets. These treatments can include inhibitors, monoclonal antibodies, or small-molecule drugs that target signaling pathways. While this is highly important for exploring the mechanism of cell death, it poses some challenges for clinical translation.We summarized published NPs targeting ferroptosis, cuproptosis, and PANoptosis (Table 5). Progress in nanomedicine is crucial for clinical translation. NPs can carry drugs specific to tumor cells and accumulate in tumor tissues, increasing their local concentration and reducing toxicity in healthy tissues. In addition, NPs can be labeled with specific fluorescent substances or contrast agents for image-guided treatment of tumors, which can achieve high-resolution imaging of tumors and guide surgery, radiotherapy, or interventional therapy. Moreover, NPs can be used as auxiliaries for tumor immunotherapy to improve the activity of immune cells and antitumor effects. For example, NPs facilitate tumor antigen display, increasing antigen-presenting cell function and triggering tumor-specific immune responses.

Lipid nanoformulations, a type of NP, are excellent drug delivery tools that deliver target ingredients within a protective outer layer of lipids. Several liposome drugs are currently on the market and are widely used to treat various tumors. For example, irinotecan and doxorubicin liposomes have been used to treat pancreatic cancer, ovarian cancer, non-Hodgkin lymphoma, myeloma, breast cancer, uterine tumors, and soft tissue sarcoma in the clinic. We also found that liposome-targeted death was critical for reprogramming the TME and regulating

Table 5 Published NPs targeting ferroptosis, cuproptosis, and PANoptosis

Cell death pathways	Nanoparticle name	Proposed mechanism	Cancer type	Related immune cells	Reference
Ferroptosis	RCH NPs	Disruption of inflammation-related immunosuppression and IFN-γ-induced PD-L1 upregulation	Melanoma	T cell↑	[240]
Ferroptosis	Pa-M/Ti-NC	·OH	Melanoma,breast cancer	CD4+ T/Treg cells, CD8+ T/Treg cells, and M1/M2 macrophages↑	[241]
Ferroptosis	H2O2/Fe3O4-PLGA	ROS	Liver cancer		[242]
Ferroptosis	ZnONPs	NCOA4	Vascular inflammation		[243]
Ferroptosis	HMPB/ML210@TA-BLM-Fe3+	ROS,GPX4	Triple negative breast cancer (TNBC)		[244]
Ferroptosis	S-biAb/dEGCG@NPs	IFN-γ,MMP-2	Glioblastoma (GBM)		[245]
Ferroptosis	PDN@AGL	ATF3/SLC7A11	Intestinal ischemia reperfusion injury	CD8+ /Tre↑	[246]
Ferroptosis	HCM@DOX	GSH,ROS	Triple-negative breast cancer (TNBC)		[247]
Ferroptosis	CuCP Lipo NPs	Lipid peroxide	Stomach cancer, colon cancer		[248]
Ferroptosis	Fe3O4-PGA-DHA	PI3K/AKT/mTOR/GPX4	Triple-negative breast cancer (TNBC)		[249]
Ferroptosis	FPBC@SN	nuclear receptor coactivator 4 (NCOA4), GPX4, IDO	Breast cancer		[187]
Ferroptosis	dGPX4@401-TK-12	GPX4	Breast cancer		[250]
Ferroptosis	Fe/ppa@PDA/B	GSH, OH	Breast cancer		[251]
Cuproptosis	NP@ESCu	ROS	Breast cance	αPD-L1	[181]
Cuproptosis	CuP/Er	GSH, Lipid peroxide	Colon adenocarcinoma, breast cancer	T cells↑	[252]
CuET NPs	Cuproptosis	GSH	NSCLC		[253]
Au25(NAMB)18 NCsCu2 + @SA/NHGs	Cuproptosis	·OH	HCC		[254]
Cuproptosis	ES@CuO	DLAT,Fe-S Cluster	Melanoma	PD-1	[255]
Cuproptosis	Cu-GA NPs	DLAT,Fe-S Cluste	Colon adenocarcinoma, breast cancer		[256]
Cuproptosis	Au@MSN-Cu/PEG/ DSF	s DLAT, LIAS, NPL4	Breast cancer		[257]
PANoptosis	PFH@Lipo-PpIX@EV	cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS)-STING	Breast cance	CD8+ and CD4+ T cells↑	[178]
PANoptosis	FCA NP	GSDMD,CASPASE-7,MLKL	Melanoma		[194]

Table 6 miRNAs target different ferroptosis players in different pathophysiological conditions

miRNAs	Cancers	Target	Effect on ferroptosis	References
miR-139	Lung cance	NRF2	Promotion	[198]
miR-137	Melanoma	glutamine transporter SLC1A5	Promotion	[199]
miR-214-3p	HCC	GPX4	Promotion	[200]
miR-15a	Prostate cancer	GPX4	Promotion	[201]
miR-670-3p	Glioblastoma	ACSL4	Inhibition	[202]
miR-19b-3p	HCC	GPX4	Inhibition	[203]
miR-1261	HCC	SLC7A11	Promotion	[204]
miR-25-3p	Prostate cancer	SLC7A11	Inhibition	[205]
miR-27a-3p	Lung cancer	SLC7A11	Promotion	[206]
miR-375	GC	SLC7A11	Promotion	[207]
miR-324-3p	Breast cancer	GPX4	Promotion	[208]
miR-455-3p	HCC	FTH1	Inhibition	[209]
miR-34a-5p	Lung cance	GTP cyclohydrolase 1	Inhibition	[210]
miR-150-5p	Colorectal cancer	c-Myb	Inhibition	[211]
miR-324-3p	Prostate carcinoma	GPX4	Inhibition	[212]
miR-432-5p	Prostate cancer	CHAC1	Inhibition	[213]
miR-1290	Glioblastoma	GPX4	Inhibition	[214]

immunotherapy efficacy. Hei et al. [196] developed a novel immunoliposome, CAR@aCD47/aPDL1-SSL, featuring encapsulated carvedilol, an adrenergic receptor inhibitor, within its lipid bilayer. The liposome surface was adorned with the ROS-responsive adapter antibodies αCD47 and αPD-L1 for enhanced functionality. This multifunctional immunoliposome significantly enhanced the antitumor effect of the immune checkpoint inhibitor αPD-L1 by reshaping the immunosuppressive TME. Hu et al. [197] prepared a matrix metalloproteinase 2 (MMP2)-responsive cascade-targeted liposome for breast cancer immunotherapy that sequentially delivered a PD-1/PD-L1 blocking peptide and an IDO1 inhibitor to reshape the immunosuppressive TME. Therefore, targeting emerging cell death through nanoengineering has great application prospects for combating tumor progression and improving the efficacy of personalized tumor treatment.

However, research on emerging forms of cell death, such as ferroptosis, cuproptosis, and PANoptosis, in the TME is limited. Many potential mechanisms are still unclear, and more basic research, such as specific cell knockout, is still needed. The construction of transgenic mouse models is crucial for exploring changes in the TME caused by immune and tumor cell death. In addition, specific targeted inhibitors and agonists must be further developed, which is also a potential challenge for subsequent translation and clinical research.

Many foreseeable opportunities exist to elucidate the regulatory mechanisms of emerging forms of cell death. Leveraging these forms of cell death in the TME holds great potential for inhibiting tumor progression and developing personalized antitumor regimens. We also predict that novel therapies based on emerging forms of cell death will soon be developed and put into clinical use, guided by specific biomarkers and precise assessment of the patient's disease background and individualized treatment (Fig. 9).

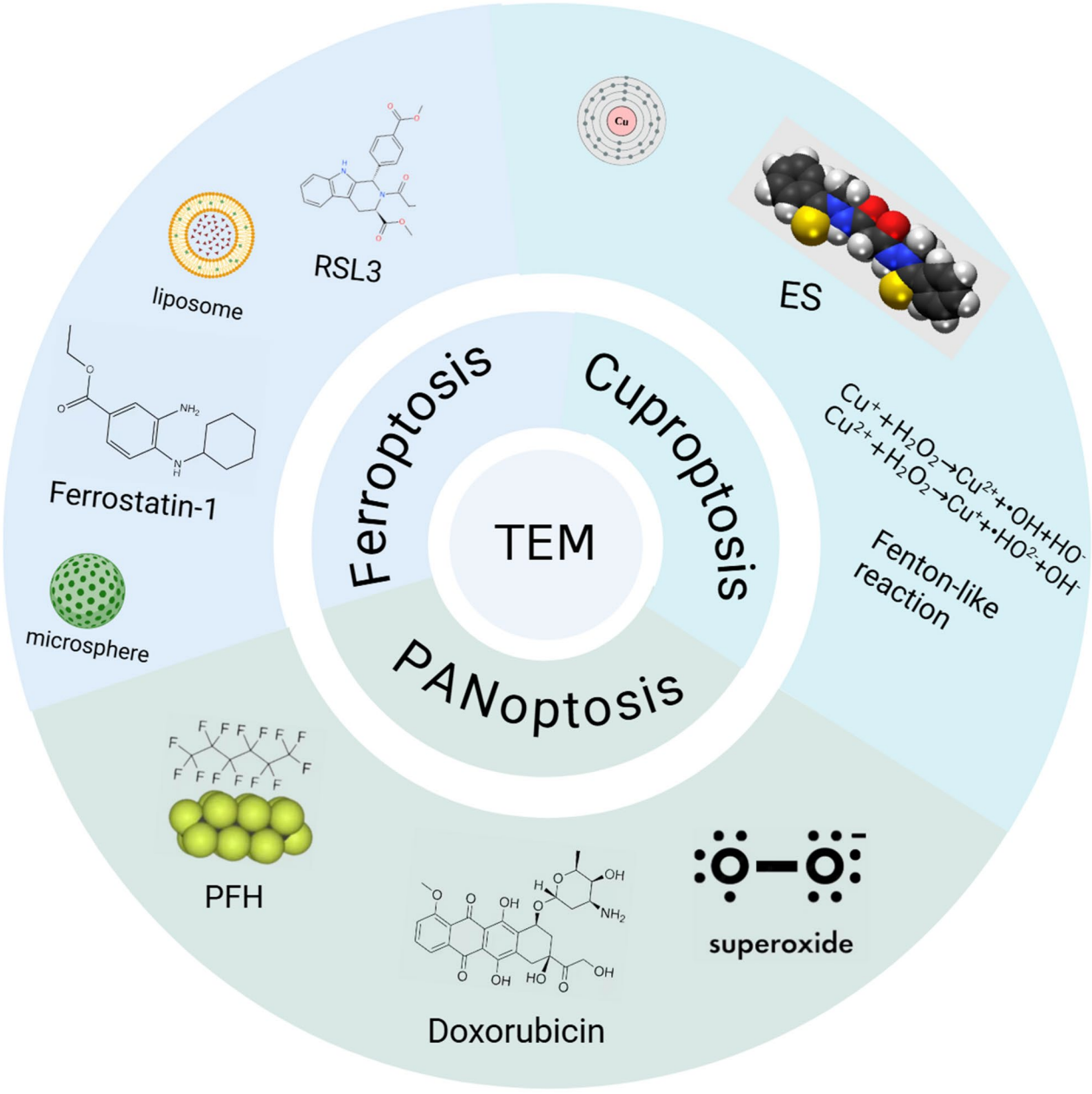

Fig. 9 Cuproptosis, ferroptosis, and PANoptosis nanoparticle-related drugs

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Author contributions
Xiaojie Zhang and Bufu Tang prepared the figures and the manuscript, including searching the literature, wring original draft and editing. Jinhua Luo, Yang Yang, Qiaoyou Weng, Shiji Fang and Zhongwei Zhao revised the details of this review. Jianfei Tu, Minjiang Chen and Jiansong Ji edited the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All of the authors are aware of and agree with the content of the paper and are listed as coauthors of the paper.

Competing interests
The authors declare no competing interests.

Declaration of competing interest
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