Targeting regulated cell death: Apoptosis, necroptosis, pyroptosis, ferroptosis, and cuproptosis in anticancer immunity

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ABSTRACT

In the evolving landscape of cancer treatment, the strategic manipulation of regulated cell death (RCD) pathways has emerged as a crucial component of effective anti-tumor immunity. Evidence suggests that tumor cells undergoing RCD can modify the immunogenicity of the tumor microenvironment (TME), potentially enhancing its ability to suppress cancer progression and metastasis. In this review, we first explore the mechanisms of apoptosis, necroptosis, pyroptosis, ferroptosis, and cuproptosis, along with the crosstalk between these cell death modalities. We then discuss how these processes activate antigen-presenting cells, facilitate the cross-priming of $CD8^+$ T cells, and trigger anti-tumor immune responses, highlighting the complex effects of novel forms of tumor cell death on TME and tumor biology. Furthermore, we summarize potential drugs and nanoparticles that can induce or inhibit these emerging RCD pathways and their therapeutic roles in cancer treatment. Finally, we put forward existing challenges and future prospects for targeting RCD in anti-cancer immunity. Overall, this review enhances our understanding of the molecular mechanisms and biological impacts of RCD-based therapies, providing new perspectives and strategies for cancer treatment.

Key words: apoptosis, necroptosis, pyroptosis, ferroptosis, cuproptosis, tumor microenvironment, anticancer immunity

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INTRODUCTION

Regulated cell death (RCD), also known as Programmed Cell Death (PCD), involves cell death regulated by specific signaling pathways.[1–3] Various forms of RCD have been identified, including apoptosis, necroptosis, pyroptosis, ferroptosis, and cuproptosis.[2,4,5] These processes play a crucial role in organism growth and development, as well as in maintaining internal homeostasis by eliminating infected, damaged, or self-destructing cells.[6] Dysregulated of RCD can contribute to the onset and progression of cancers.[1,7] Resistance to cell death is one of the hallmarks of tumors and a key mechanism of tumor resistance to therapy.[1] Targeting RCD has been shown

to not only directly destroy tumor cells but also enhance the organism's anti-tumor immunity, presenting promising clinical prospects for cancer therapy.[8–11]

The immune system is integral to preventing tumor development, progression, and metastasis, as well as modulating responses to treatment.[12–14] It has been reported that tumor cells undergoing RCD can release tumor-associated antigens (TAAs), damage-associated molecular patterns (DAMPs), and pro-inflammatory cytokines, which elicit secondary immunity and affect the tumor immune microenvironment.[15–17] These effects may enhance immunostimulation or disrupt immunosuppression, leading to T-cell activation, dendritic cell (DC) maturation, proliferation, and tumor infiltration, potentially acting synergistically with existing immunotherapies.[18,19] RCD has multiple effects on the immune response,[5,20] RCD exerts a suppressive effect on immune response. For instance, during apoptosis, the activation of caspases leads to the downregulation of proteins such as cyclic GMP-AMP synthase (cGAS), MAVS, and interferon regulatory factor 3 (IRF3), which are essential for the activation of innate immunity.[21] These studies suggest that a summary of the relationship between RCD and tumor immunity is necessary to provide precisely targeted guidance for tumor immunotherapy.

Tumor cells evade immune surveillance by reducing their immunogenicity and establishing immunosuppressive networks. Immunotherapies, including immune checkpoint blockade (ICB), chimeric antigen receptor T (CART) cells, cytokine therapy, and dendritic cell vaccines, are designed to stimulate anti-tumor immune responses.[22–24] However, some patients exhibit a limited response to immunotherapy. Several studies have demonstrated that immunotherapies can have synergistic effects when combined with radiotherapy and chemotherapy.[25,26] Consequently, the combination of immunotherapy with other treatment modalities is gaining significant attention.[27,28] Moreover, targeting RCD can enhance the efficacy of immune checkpoint inhibitors like anti-PD-1 antibodies, thereby improving anticancer outcomes.[23] Given the immunomodulatory effects of RCD, therapies that focus on RCD present a promising strategy to synergistically enhance immunotherapy and inhibit tumor development.[29–31] Therefore, it is highly desirable to review the potential of targeting RCD to synergize with anticancer immunity.

Currently, our understanding of the interactions among various RCD pathways remains limited. Additionally, the potential applications of these types of RCD in anticancer immunity have yet to be thoroughly explored. This gap presents a critical area for future research that could lead to significant breakthroughs in cancer treatment strategies. In this review, we first delineate the molecular mechanisms of five different types of RCD, including apoptosis, necroptosis, pyroptosis, ferroptosis, and the recently discovered cuproptosis, along with their crosstalk. Next, we discuss their role in the anti-tumor immune response. We also summarized numerous clinically approved drugs that can suppress tumors by inducing RCD and affecting antitumor immunity. Finally, we discuss existing challenges and future prospects for targeting RCD in anticancer immunity.

CORE MOLECULAR MECHANISMS OF DIFFERENT CELL DEATH

Apoptosis

Apoptosis, the earliest identified form of RCD,[32] is characterized by distinct morphologic features, including cell shrinkage, chromatin condensation, and tight packaging of organelles and cytoplasm.[33] This process is mediated by caspases, a family of cysteine-aspartic proteases that cleave specific target proteins, leading to the formation of apoptosome.[34] Eventually, apoptosomes are rapidly phagocytosed by adjacent cells.[34]

Mechanistically, apoptosis can be initiated via two main pathways: the intrinsic and extrinsic pathways.[35] The intrinsic pathway, also known as the mitochondrial pathway, is triggered by intracellular stressors such as DNA damage, growth factor or nutrient deprivation, and endoplasmic reticulum (ER) stress.[33,36] Key processes of apoptosis are subsequently activated, encompassing the induction of mitochondrial outer membrane permeabilization (MOMP) and the release of soluble proteins, such as Cytochrome c, through the pore formed in the mitochondrial outer membrane.[37,38] MOMP is tightly regulated by the BCL-2 family proteins, which include effector proteins (BAX and BAK) , pro-apoptotic BH3-only proteins, and anti-apoptotic proteins, such as BCL-2, BCL-X_L, BCL-W, BCL-2-A1 and MCL1.[39–41] Cytochrome c, released from the intermembrane space, binds and activates the adaptor molecule apoptotic protease-activating factor 1 (APAF1).[42] This activation leads to the oligomerization of APAF1 and the recruitment of pro-caspase 9, forming a complex known as the apoptosome.[43] The activation of caspase 9 then catalyzes the cleavage and activation of executioner caspases 3 and 7, ultimately resulting in apoptosis.[44–46]

The extrinsic pathway also referred to as the death receptor pathway, provides an alternative route for the activation of caspases 3 and 7 through the mediation of caspase 8.[47] Ligands such as Fasl, tumor necroptosis factor (TNF), or TNF-related apoptosis-inducing ligand (TRAIL) bind to

their corresponding receptors FasL, TNFR1/TNFR2, and death receptor 4 (DR4)/DR5 on the plasma membrane respectively.[48–51] Upon ligand binding, adaptor molecules FAS-associated *via* the death domain (FADD) and TNFRSF1A-associated via the death domain (TRADD) are recruited to the receptor complex.[52] These adaptors contain death domains that facilitate the recruitment of pro-caspase 8 to the death-inducing signaling complex (DISC), where caspase 8 is activated.[52] The activation of caspase 8 subsequently leads to the cleavage and activation of caspase 3/7, ultimately triggering apoptosis (Figure 1A).[53]

Necroptosis

Necroptosis has been identified as an alternative form of cell death to apoptosis, mediated by the engagement of death domain receptors by their respective ligands.[54,55] The morphologic characteristics of necroptosis include cell swelling, ruptured plasma membrane, and loss of cellular and organelle integrity. The passive leakage of intracellular contents resulting from membrane rupture ultimately leads to inflammation and immune responses.[56]

The necroptotic pathway can be initiated by activating RIPK3 through various death domain receptors that recruit their corresponding adaptor proteins. RIPK3 contains a C-terminal RIP homotypic interaction motif (RHIM), which is crucial for its activation and for mediating the initiation of necroptosis.[57] Upon binding of TNF to TNFR1, complex I is formed, which includes TRADD, FADD, RIPK1, TRAF, and cIAP1 and cIAP2. In cases where caspase 8 activity is inhibited, RIPK1 binds to RIPK3 through the shared RHIM, thereby facilitating the recruitment of additional RIPK3 molecules to form an initial RIPK1-RIPK3 heterodimeric complex.[55,58–61] This concentration of RIPK3 not only promotes homodimeric interactions among RIPK3 molecules but also activates RIPK3 through autophosphorylation. Furthermore, TRIF-dependent Toll-like receptors (TLR3 and Toll-like receptor 4 [TLR4]) can activate RIPK3 through RHIM-dependent interactions.[62,63] Additionally, the interferon (IFN)-independent expression of the DNA-dependent activator of IFN regulatory factors, DAI (also known as ZBP1 or DLM-1), contains an RHIM that can activate RIPK3.[64] Subsequently, activated RIPK3 phosphorylates mixed lineage kinase domain-like protein (MLKL). Following phosphorylation, oligomerized MLKL (pMLKL) forms the "necrosome" complex, which then translocates to the plasma membrane.[65,66] This translocation increases plasma membrane permeability, leading to membrane rupture and the release of DAMPs.[67] Consequently, necroprosis occurs, triggering inflammatory and immune responses (Figure 1B).

Pyroptosis

Proinflammatory PCD, first identified in macrophages following pathogen infection, was termed pyroptosis in 2001 by Brad T. Cookson and his colleagues.[68] Pyroptosis is characterized by cell swelling, lysis, and the release of many proinflammatory factors.[69,70] Additionally, pyroptosis involves DNA damage and chromatin condensation, features that are reminiscent of apoptosis.[71] Pyroptosis is executed by inflammasome-activated gasdermin (GSDM), a member of a large family of proteins known for their novel membrane pore-forming activity.[72,73] Mechanistically, GSDMs are cleaved by caspases, which liberate the pore-forming domain (PFD) from the repressor domain, resulting in the formation of pores in the cell membrane.[74,75]

Current research has confirmed that the activation of pyroptosis can occur through multiple pathways.[5,69] Pyroptosis resulting from cleavage of GSDMD by caspase 1, 4, 5, and-11, is one of the main approaches.[76,77] Pathogens-associated molecular patterns (PAMPS) and DAMPs initiate the activation of NLRP3 inflammasome, which then recruits and activates caspase 1.[78] The cleavage of GSDMD by caspase 1 leads to the formation of pores in the plasma membrane and the release of IL-1β and IL-18, resulting in pyroptosis through the canonical pathway.[79] Moreover, caspase 11 in mice and caspase 4/5 in humans can directly bind lipopolysaccharide (LPS) in response to LPS exposure, leading to GSDMD cleavage and subsequent pyroptosis *via* a non-canonical pathway.[80–82] Furthermore, ESCRT-dependent membrane repair mechanisms can inhibit pyroptosis downstream of GSDMD activation.[83]

Multiple studies are discovering that other GSDMs also form cytotoxic pores and implicate GSDMs in various pathways of pyroptosis.[84] Notably, in instances where the canonical NLRP3 pathway is inhibited, pyroptosis can still be induced in macrophages through the cleavage of GSDME by caspase 3.[85,86] Specifically, the cleavage of GSDMC by caspase 8 following TNFα treatment can also induce pyroptosis.[87] Additionally, pyroptosis may be triggered by the cleavage of GSDMB by GZMA from cytotoxic lymphocytes.[88,89] Additionally, the streptococcal pyrogenic exotoxin B (SpeB), a protease virulence factor secreted by the major human pathogen group A Streptococcus (GAS), cleaves GSDMA and triggers pyroptosis.[90,91] These findings suggest that the gasdermin family likely serves as pivotal effectors of pyroptosis (Figure 1C).[92,93]

Ferroptosis

Ferroptosis is an iron-dependent form of cell death characterized by lipid peroxidation in the plasma membrane.[7,94–96] Morphologically, it is marked by reduced mitochondrial volume, fractured mitochondrial outer

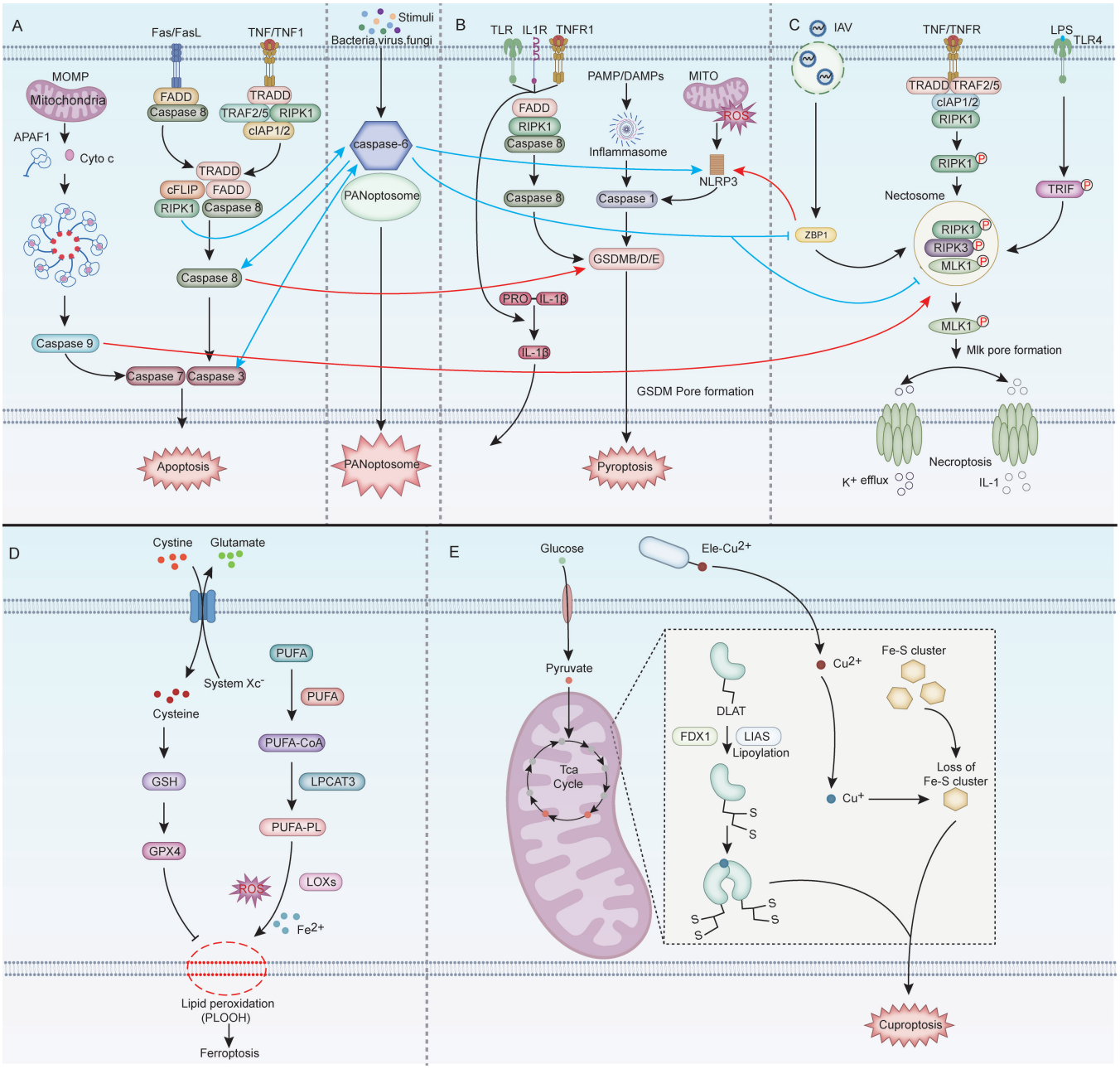

Figure 1: Molecular mechanisms and crosstalk among five cell death modalities: Apoptosis, Necroptosis, Pyroptosis, Ferroptosis, and Cuproptosis. (A) Apoptosis is a programmed form of cell death executed by activating intrinsic (mitochondrial pathway) and extrinsic (death receptor pathway) signaling pathways. These pathways ultimately activate caspases, enzymes that degrade key proteins within the cell, leading to orderly cellular disassembly and death. (B) Necroptosis is a controlled form of necrosis, considered an alternative to apoptosis, particularly when apoptotic pathways are inhibited. It is facilitated by activating specific signaling proteins, such as RIPK1, RIPK3, and MLKL, promoting cell membrane rupture and subsequent leakage of cellular contents. (C) Pyroptosis is a form of cell death dependent on inflammasomes and caspases (such as Caspase-1, Caspase-4, Caspase-5, Caspase-11). This form of death involves gaseous swelling, ultimately leading to cell membrane rupture and the release of inflammatory mediators like IL-1β and IL-18.(D) Ferroptosis is a form of cell death driven by iron-dependent oxidative stress. Its hallmark is the accumulation of lipid peroxidation within the cell, primarily caused by uncontrolled iron-catalyzed reactions, leading to the loss of cell membrane integrity. (E) Cuproptosis is a form of cell death induced by copper. Copper ions directly interact with multiple mitochondrial fatty acid dehydrogenases, leading to protein aggregation and inactivation, thereby impairing mitochondrial function, and resulting in cell death. Caspase-6 plays a critical crosstalk role in PANoptosis, mutually activating with caspase-3/7 and cleaving downstream caspase-8 to promote apoptosis. It also facilitates apoptosis by cleaving RIPK1 and promotes necroptosis through interaction with RIPK3. Additionally, caspase-6 triggers the activation of the NLRP3 inflammasome mediated by ZBP1, regulating pyroptosis. Caspase-8 directly cleaves GSDMD to induce pyroptotic cell death, while caspase-9 promotes extrinsic apoptosis. GSDMD acts as an executor of multiple cell death pathways; ROS are implicated in triggering both ferroptosis and pyroptosis; Iron overload, a critical driver of ferroptosis, facilitates the opening of the mitochondrial permeability transition pore (MPTP), intensifying RIP1 phosphorylation and leading to necroptosis.

membranes, diminished mitochondrial cristae, and a normal-size nucleus without chromatin condensation.[97] Under normal physiological conditions, a delicate balance among iron, ROS, and lipids is crucial for cellular function. However, disruption of this balance leads to lipid peroxidation that surpasses the capacity of internal antioxidants, ultimately resulting in ferroptosis.[98–100]

A key aspect of ferroptosis is that free polyunsaturated fatty acids must be esterified to membrane phospholipids to induce lethality upon peroxidation.[101] Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) are the main enzymes involved in the biosynthesis and esterification of polyunsaturated fatty acid phospholipids (PUFA-PLs), respectively.[7] Iron serves as a cofactor for the lipoxygenase (LOX) family or NADPH-cytochrome P450 reductase (POR), facilitating enzymatic lipid peroxidation.[102–104] Furthermore, Fe^{2+}, as an unstable form of iron, can participate in Fenton and Fenton-like reactions, catalyzing the formation of free radicals that contribute to non-enzymatic lipid peroxidation.[105,106] Enhanced iron uptake through the transferrin receptor (TFRC) promotes ferroptosis.[107] Additionally, the degradation of the intracellular iron exporter SLC40A1/ferroportin-1 enhances susceptibility to ferroptosis *in vitro*.[108,109] Nuclear receptor coactivator 4 (NCOA4)-induced ferritin autophagy, also known as ferritinophagy, selectively degrades ferritin, elevating intracellular iron levels and accelerating lipid peroxidation, thereby promoting ferroptosis.[110]

Glutathione (GSH), a component of the cellular antioxidative system, is essential in eliminating excessive ROS.[111] Inhibition of the cystine-glutamate antiporter system Xc- leads to GSH depletion and inactivation of the glutathione-dependent lipid hydroperoxidase glutathione peroxidase 4 (GPX4). GPX4, which depends on GSH as a reducing cofactor, functions to prevent ferroptosis.[112,113] The GSH-GPX4 axis is currently regarded as the most important mechanism for resisting ferroptosis. Additionally, three alternative mechanisms exist that resist ferroptosis independently of GPX4. Ferroptosis suppressor protein 1 (FSP1) mitigates ferroptosis mediated by ubiquinone.[114] Furthermore, the enzyme dihydroorotate dehydrogenase (DHODH) reduces CoQ to CoQH2 in the mitochondrial inner membrane, thereby alleviating ferroptosis, particularly in cases of mitochondrial GPX4 deficiency.[108] Recent evidence also indicates that the enzyme MBOAT1/2 inhibits ferroptosis by selectively increasing cellular levels of PE-MUFA while reducing cellular levels of PE-PUFA. This anti-ferroptosis pathway operates independently of GPX4 or FSP (Figure 1D).[115]

Cuproptosis

Cuproptosis, a term introduced by Peter Tsvetkov and colleagues in 2022, describeds a newly discovered form of RCD that relies on the accumulation of intracellular copper.[116] Unlike other forms of RCD, which are typically characterized by distinctive morphological changes, the morphological features of cells undergoing cuproptosis remain undefined, necessitating further research.[117]

Copper is a trace element essential to various signaling pathways and tumor-related pathophysiology within the human body.[118] The cytotoxicity of the copper ionophores is attributed to the accumulation of intracellular copper rather than the carrier itself.[116] For a long time, the mechanism by which elesclomol, a copper ionophore, transports excess copper ions into cells to induce cell death has been a subject of controversy, with many researchers categorizing this process as apoptosis.[119,120] However, recent studies have established cuproptosis as a distinct, non-apoptotic form of cell death that is closely associated with mitochondrial respiration and the lipoic acid (LA) pathway. Mechanistically, elesclomol facilitates the transport of Cu (Ⅱ) into mitochondria, directly targeting the mitochondrial enzyme ferredoxin 1 (FDX1), which reduces Cu (Ⅱ) to the more toxic Cu (Ⅰ). Subsequently, Cu (Ⅰ) binds immediately to lipoylated DLAT, a component of the tricarboxylic acid (TCA) cycle, promoting the oligomerization of lipoylated DLAT and destabilizing iron-sulfur (Fe-S) cluster proteins. This destabilization leads to proteotoxic stress and ultimately results in cell death.[116]

As a novel type of RCD, our understanding of cuproptosis is still limited. Nonetheless, existing research suggests that targeting cuproptosis could represent a potentially effective treatment strategy for eliminating tumors. Further investigations are crucial to fully elucidate the mechanisms and cellular morphology associated with cuproptosis, as well as to identify specific inducers and inhibitors of this cell death pathway (Figure 1E).

Crosstalk among components of RCD

RCD pathways do not appear to be isolated signaling cascades. Evidence indicates that pathways regulating different RCD patterns exhibit crosstalk at various levels.[5] For example, the pathways of apoptosis, necroptosis, and pyroptosis (collectively referred to as PANoptosis) can transform into one another under certain conditions.[121] Research has revealed that caspase-6 plays a crosstalk role in the mechanistic pathway among PANoptosis.[121] In apoptosis, caspase-3 activates caspase-6, which subsequently cleaves downstream caspase-8, underscoring its critical role in this process.[122] Additionally, caspase-6 can be activated by caspase-3/7 and can reciprocally activate these caspases during apoptosis, thereby establishing itself as both an

initiator and executor within the apoptotic pathway.[123,124] Caspase-6 also plays a dual role in regulating necroptosis. It has been reported to promote apoptosis by cleaving RIPK1, which in turn inhibits necroptosis by suppressing the production of inflammatory cytokines.[125] Conversely, caspase-6 can promote necroptosis through its interaction with RIPK3, facilitating the binding of RIPK3 and ZBP1.[126] Furthermore, caspase 6 promotes ZBP1-mediated activation of NLRP3 inflammasome, which mediates pyroptosis.[121,126–131] Notably, the caspase family plays a significant role in the regulation of various cell death.[132] In particular conditions, caspase-8, traditionally viewed as an apoptosis initiator, can directly cleave GSDMD to induce pyroptosis.[133,134] Similarly, caspase-9, which is involved in the initiation of extrinsic apoptosis, is essential for necroptosis and regulates the formation of the necrosome.[135]

Studies have demonstrated that GSDMD serves as an executioner for multiple cell death pathways.[136,137] In Lrrk2G2019S macrophages, mitochondrial ROS guides GSDMD to mitochondria following inflammasome activation, where mitochondrial GSDMD (mito-GSDMD) converts cell death from pyroptosis to necroptosis.[138] ROS are implicated in triggering both ferroptosis and pyroptosis.[139] Elevated levels of ROS also promote the activation of the NLRP3 inflammasome, leading to pyroptosis.[140,141] Furthermore, inducers of ferroptosis have been found to cause ER stress and enhance the expression of the pro-apoptotic molecule PUMA without triggering apoptosis.[142] Iron overload, a key driver of ferroptosis, facilitates the opening of the mitochondrial permeability transition pore (MPTP) , which exacerbates RIP1 phosphorylation and leads to necroptosis.[143] Additionally, ferroptosis inducers, such as sorafenib and erastin have been shown to promote cuproptosis by inhibiting system Xc-, thereby downregulating intracellular GSH synthesis, as GSH acts as a copper chelator.[144] Recent findings also indicate that copper-driven cascade can trigger the maturation of dendritic cells and initiate intense T cell-mediated pyroptosis,[145] highlighting the role of copper in pyroptosis (Figure 1). However, whether copper-dependent cuproptosis is associated with ferroptosis, pyroptosis and other RCD still needs further investigations.

THE ROLE OF RCD IN CANCER IMMUNE RESPONSE

Apoptosis in anti-tumor immunity

Cell death modalities are classified based on their immunogenic potential into non-immunogenic types, such as apoptosis, and immunogenic types, such as necroptosis, pyroptosis, ferroptosis, and cuproptosis. Unlike other forms of cell death, apoptotic cells typically cleared rapidly by phagocytes are traditionally considered incapable of activating innate immunity and instead possess anti-inflammatory properties, a phenomenon referred to as "innate immune tolerance", crucial for normal physiological processes within the organism.[146] Previous studies have shown that during apoptosis, mitochondrial DNA (mtDNA) and cytochrome c are released into the cytoplasm, where the mtDNA robustly activates the cGAS-stimulator of interferon genes (STING) pathway, leading to IFN-I production and inflammatory responses. In 2014, publications from the teams of Richard Flavell and Benjamin Kile concurrently highlighted the pivotal role of apoptotic caspases in maintaining this innate immune silence.[147,148] Subsequent research by Jiang Z and colleagues demonstrated that activated CASP3/6/7 can effectively block mtDNA-induced cGAS-STING activation by cleaving cGAS and IRF3, thereby preventing IFN-I production and inflammatory responses.[21] Additionally, cleavage of MAVS and IRF3 thoroughly blocks RIG-I-MAVS mediated innate immune activation. These findings elucidate how apoptosis ensures the critical aspect of "innate immune silence". Caspases have also been shown to indirectly inactivate DAMPs, such as HMGB1.[149] Blocking caspases in conjunction with MOMP can activate NF-κB and induce a mitochondrial DNA-mediated TFN-I response, thus triggering a robust ICD.[147,150] Consistently, caspase inhibition has been shown to induce anti-tumor activity and lead to tumor regression.

However, under specific conditions, apoptotic cells can exhibit immunogenic properties. For example, certain anti-tumor therapies, including chemotherapeutic drugs, gamma-irradiation, or photodynamic therapy, can induce a specific form of apoptosis with immunostimulatory or adjuvant-like properties, termed immunogenic apoptosis (IA).[151] The stimulatory effects of chemotherapeutic drugs and ionizing radiation may mobilize pattern recognition receptors (PRRs) such as cGAS.[17,151] In such cases, increased mitochondrial membrane permeability following therapy can activate the cGAS-stimulator of the IFN genes pathway, leading to the release of mitochondrial DNA.[19] Additionally, during cancer therapy, the phagocytic capacity of phagocytes may be overwhelmed by a large number of dying cells. This can lead to secondary necrosis of apoptotic cells, subsequent release of DAMPs into the microenvironment, and thereby provoking inflammation and immune responses.[152]

Necroptosis in anti-tumor immunity

Necroptosis plays a crucial role in stimulating tumor immunogenicity and enhancing anti-tumor immunity.[153] This form of cell death not only triggers the activation and assembly of death-inducing proteins but also stimulates the transcription of danger signals, which are

subsequently released into the tissue microenvironment upon cell dissolution. The DAMPs released by tumor cells undergoing necroptosis activate DCs, leading to the maturation and activation of $CD8^+$ T cells, thereby enhancing their tumor-killing function.[154] The immunogenicity of necroptosis largely depends on the synergistic action of RIPK1 activation and NF-κB signal transduction.[155] The activation of RIPK1 and RIPK3 not only contributes to the transcriptional induction of DAMPs, which is then dissolved and released through MLKL-mediated cell rupture, but also triggers NF-κB and IFN signaling pathways.[155–157] As the release of intracellular DAMPs promotes inflammation, necroptosis is also considered an inflammatory form of cell death. For instance, in cervical cancer cells, tumor cells undergoing necroptosis release IL-1α, a necessary precursor for DCs' production of IL-12, which is essential for anti-tumor responses.[158] Similarly, the release of IL-1α and the activation of DCs are strictly dependent on RIPK3 expression in tumor cells. The NF-κB signaling pathway induces the production of cytokines such as TNF, immune-inducing factors like CC chemokine ligand 2 (CCL2), CXC chemokine ligands 1/8/9 (CXCL1/8/9), and members of the IL-6 and IL-1 families, and IFN-1.[159] Additionally, research by Yatim *et al.* underscores the necessity of NF-κB in initiating immune responses and its interplay with the TME during necroptosis.[155] In necroptosis, the inflammatory mediators released from dying cells are insufficient to activate $CD8^+$ T cells alone, and decoupling NF-κB signaling from necroptosis reduces the efficiency of initiating immune responses. MLKL expression in tumors significantly boosts T cell immunity against tumor neoantigens, leading to a marked increase in antitumor activity.[160,161] Recent studies have shown that the activation of the ZBP1-MLKL pathway can regulate the release of mitochondrial DNA following radiotherapy, significantly boosting the anti-tumor immune response, and offering a new therapeutic strategy to counteract radiation therapy resistance.[162] Notably, a study demonstrated that in a mouse tumor model lacking DAMP receptor expression, fibroblasts undergoing necroptosis still suppressed tumor growth. This suggests that fibroblasts within the TME can contribute to immune responses through necroptosis, independent of DAMP release mediated by MLKL-dependent cell lysis (Figure 2).[154]

Pyroptosis in anti-tumor immunity

Pyroptosis is an autonomous form of PCD that triggers inflammatory responses, characterized by the progressive swelling and eventual rupture of the cell membrane, leading to the release of cellular contents and the activation of immune responses. This inflammatory mechanism plays a crucial role in various diseases and is pivotal in cancer immunotherapy. In 2020, Judy Lieberman and colleagues reported that granzyme B (GZMB) from natural killer (NK) cells could directly cleave GSDME, activating pyroptosis in cancer cells, further stimulating antitumor immune responses, and inhibiting tumor growth.[163] Upon activation, GSDM proteins perforate the cell membrane, causing pyroptosis and releasing numerous cytokines and danger signal molecules, which activate the immune system and provoke inflammatory responses. Even a minor proportion of tumor cells undergoing pyroptosis can significantly modulate the tumor immune microenvironment, activating potent T cell-mediated antitumor immune responses that reduce tumor size.[164]

Pyroptosis is closely associated with inflammatory responses, with dying cells releasing IL-1 family cytokines and HMGB1. IL-1β and IL-18, both members of the IL-1 family, are major pro-inflammatory cytokines released through Caspase-1 activation during immune cell pyroptosis. IL-1β is known to inhibit mesenchymal-epithelial transition (MET) in tumor cells, enhance T cell antigen recognition, and promote the proliferation of antigen-specific $CD8^+$ T lymphocytes.[165–167] IL-18 enhances the ability of T cells stimulated by anti-CD3 to produce IFN-γ, which exerts antitumor effects by inhibiting the secretion of immunosuppressive cytokines by regulatory T cells (Tregs) and triggering the activation and proliferation of $CD8^+$ T lymphocytes, inducing the production of GZMB, activating apoptotic proteins, and degrading anti-apoptotic proteins to eliminate cancer cells.[168–170] Besides IL-1β and IL-18, HMGB1 interacts with TLR4 to activate macrophages and secrete tumor necrosis factor, facilitating innate immune responses. HMGB1 also participates in the migration of mature DCs, inducing cytotoxic T-cell infiltration and MHC-II upregulation in DCs, thereby enhancing antitumor activity.[171–173] Furthermore, the release of IL-6 from pyroptotic cells contributes to adaptive responses by increasing cell migration, differentiation, and $CD8^+$ T cell antibody production, inhibiting Treg differentiation, and preventing macrophage death.[174] These inflammatory cytokines largely exert their antitumor effects by influencing cytotoxic lymphocytes or modifying the tumor microenvironment to mobilize a stronger immune response.

The GSDM protein family is central to pyroptosis and functions as tumor suppressor genes.[175] GSDMB triggers pyroptosis either through its own cleavage or by inducing the cleavage of GSDMD. On one hand, IFN-γ secreted by NK cells or $CD8^+$ T lymphocytes can upregulate the expression of GSDMB in esophageal and colorectal adenocarcinoma cells. Subsequently, GSDMB is cleaved by granzyme A, triggering pyroptosis and facilitating tumor clearance. On the other hand, GSDMB can also engage in the non-canonical pathway of pyroptosis by enhancing

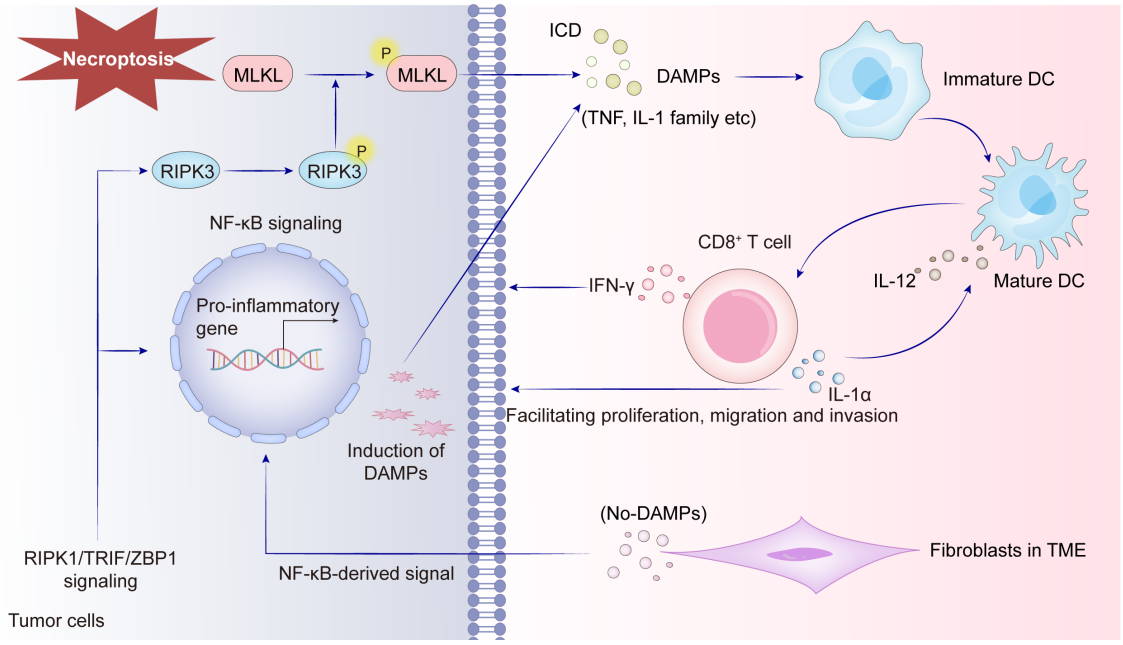

Figure 2: Necroptosis in Tumor Immunity. The immunogenicity of necroptosis largely depends on the synergistic action of RIPK1 activation and NF-κB signaling. Tumor cells undergoing necroptosis release DAMPs (such as TNF and the IL-1 family), which activate dendritic cells (DCs), leading to the maturation and activation of CD8⁺ T cells and enhancing their tumor-killing function. Tumor cells promote anti-tumor responses by releasing IL-1α, which stimulates DCs to produce IL-12. Additionally, fibroblasts within the tumor microenvironment can contribute to the immune response through necroptosis, independent of MLKL-dependent cytolysis-mediated DAMP release.

Caspase-4 activity and the cleavage of GSDMD.[88,176] Studies have shown that even with intact Caspase-1, shRNA knockdown of GSDMD in mouse bone marrow-derived macrophages inhibits pyroptosis and downregulates IL-1β levels.[77] Additionally, the amount of GSDMD in cytotoxic T lymphocytes (CTLs) correlates positively with their cytotoxic response against lung cancer cells. In activated CTL OT-1 cells, upregulation of GSDMD aligns with CD8A, GZMB, and IFNG, markers of CD8⁺ T lymphocytes.[177] CD8⁺ T cells, by secreting GZMA and GZMB, cleave GSDMB/D/E, thereby inducing pyroptosis in cancer cells.[29,178] Furthermore, CTL-induced pyroptosis is mediated by Caspase-4. Consequently, in the non-small cell lung cancer cell line H1299, shRNA-mediated silencing of Caspase-4 diminishes CTL activation and GSDMD-induced pyroptosis. Beyond lung cancer, downregulation of GSDMD correlates with reduced cytolysis in the ovalbumin-expressing Lewis lung cancer cell line 3LL-OVA.[177] Increased expression of GSDME enhances phagocytosis of tumor cells by tumor-associated macrophages (TAM) and augments the quantity and functionality of NK cells and CD8⁺ T lymphocytes within the tumor milieu.[163] Notably, CD8⁺ T cells facilitate the delivery of ribonuclease A (RNase A) and GZMB into tumor cells, which activates the caspase-3 and GSDME pathways, leading to enhanced CD8⁺ T cell-mediated immunotherapy.[179] Therefore, addressing how to mitigate the negative effects and harness the tumor-suppressive potential of dual-function proteins like GSDMD presents a pressing challenge (Figure 3).

Ferroptosis in anti-tumor immunity

Ferroptosis in tumor cells can reshape the tumor immune microenvironment, and conversely, immune cells can induce ferroptosis in tumor cells, thereby exerting an anti-tumor effect. There is a complex interplay between ferroptosis in tumor cells and immune cells. Research by Efimova *et al.* found that the agent RSL3 enhances the proliferation, activation, and immune efficacy of murine dendritic cells in a time-dependent manner, primarily associated with ATP and HMGB1 released by tumor cells.[180] In the early stages of ferroptosis, however, tumor cells inhibit DC's maturation and antigen-presenting function.[181] Photodynamic therapy (PDT)-induced ferroptosis also promotes the release of HMGB1 and ATP from tumor cells.[180]

GPX4, an intracellular enzyme regulating phospholipid peroxidation, not only supports the survival and proliferation of CD4⁺ and CD8⁺ T cells but also acts as a regulator of ferroptosis, protecting activated Tregs from ferroptosis and playing a crucial role in suppressing anti-tumor immunity.[182,183] Studies have shown that CD8⁺ T cells activated by PD-L1 immunotherapy secrete IFN-γ, which downregulates the expression of the SLC3A2 and SLC7A11 subunits of system Xc-, reducing cystine uptake in bladder cancer cells, increasing lipid peroxidation levels,

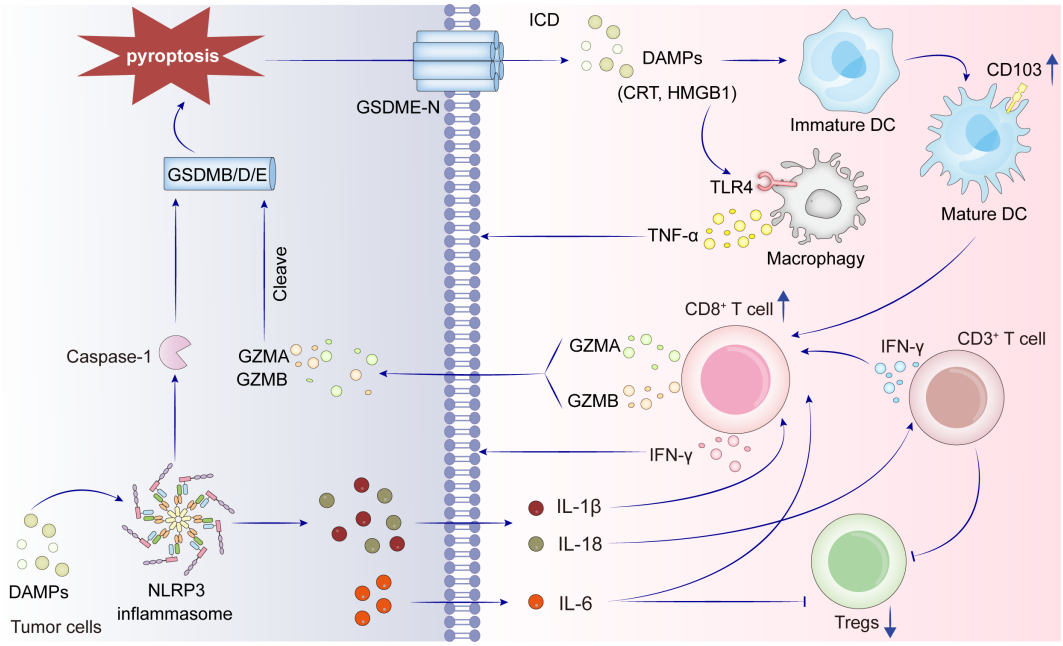

Figure 3: Pyroptosis in Tumor Immunity. Cells undergoing pyroptosis release IL-1 family cytokines (IL-1β and IL-18) and HMGB1, which further trigger the activation and proliferation of CD8⁺ T lymphocytes. IL-1β inhibits tumor cell mesenchymal-epithelial transition (MET), enhances T cell antigen recognition, and promotes specific CD8⁺ T lymphocyte proliferation; IL-18 enhances the ability of anti-CD3 stimulated T cells to produce IFN-γ, by inhibiting the secretion of immunosuppressive cytokines from Treg cells, and triggers the activation and proliferation of CD8⁺ T lymphocytes, inducing GZMB production, activating caspases, and degrading anti-apoptotic proteins to eliminate cancer cells. HMGB1 interacts with Toll-like receptor 4 (TLR4), activating macrophages and promoting the secretion of tumor necrosis factor to enhance the innate immune response. The release of IL-6 facilitates the adaptive immune response by increasing cell migration, differentiation, and CD8⁺ T cell antibody production, inhibiting Treg cell differentiation, and preventing macrophage apoptosis. CD8⁺ T cells induce tumor cell pyroptosis by secreting GZMA and GZMB, which cleave GSDMB/D/E.

and sensitizing these cells to ferroptosis.[184] Additionally, IFN-γ released by CD8⁺ T cells, in conjunction with polyunsaturated fatty acid arachidonic acid in the tumor microenvironment, activates ACSL4, altering lipid composition and inducing immunogenic ferroptosis in tumor cells.[185] Multiple studies on targeted ferroptosis combined with ICB therapy also demonstrate that inducing tumor cell ferroptosis, when combined with anti-PD-1 antibody therapy, exhibits strong anti-tumor effects.[186]

CD36 is a fatty acid transport receptor that mediates the recognition and transmembrane transport of fatty acids. Significantly elevated levels of CD36 expression are observed on the surfaces of tumor-infiltrating Tregs and CD8⁺ T cells. Tumor-infiltrating CD8⁺ T cells intake fatty acids in a CD36-dependent manner, leading to the accumulation of lipid peroxides within the cells and promoting ferroptosis in these cells.[187] Administering a CD36 monoclonal antibody to melanoma-bearing mice reduces tumor-infiltrating Tregs and increases infiltrating CD8⁺ T cells, thereby significantly inhibiting tumor growth.[188] Thus, targeting CD36 can reshape the composition and function of T cells in the TME through the ferroptosis pathway.

The ovarian tumor domain-containing protein 1 (OTUD1) is involved in the deubiquitination of iron-responsive element-binding protein 2 (IREB2), stabilizing IREB2 to enhance iron transport mediated by transferrin receptor 1 (TFR1). This process increases the production of reactive oxygen species, promoting ferroptosis in colorectal cancer cells. Furthermore, colorectal cancer cells overexpressing OTUD1 facilitate the release of DAMPs, attracting tumor-reactive T cells and thus limiting the progression of colon cancer.[189] Therefore, high expression of OTUD1 promotes ferroptosis in colon cancer cells *via* the OTUD1-IREB2-TFR1 signaling axis, while also enhancing the cytotoxic effects of T cells.[189] Consequently, ferroptosis plays a significant role in T cell-mediated antitumor immunity, impacting the efficacy of immunotherapies.

Macrophage phenotypes and functions are influenced by their surrounding microenvironment. M1 macrophages express high levels of inducible nitric oxide synthase (iNOS) and produce significant amounts of NO, which inhibits lipid peroxidation and resists ferroptosis. In contrast, M2 macrophages are susceptible to ferroptosis inducers and can transition to the M1 phenotype *via* ferroptotic pathways, reshaping the tumor immune microenvironment and enhancing the efficacy of anti-PD-1 immunotherapy in hepatocellular carcinoma.[190] The use of ferroptosis inducers, such as erastin, sorafenib,

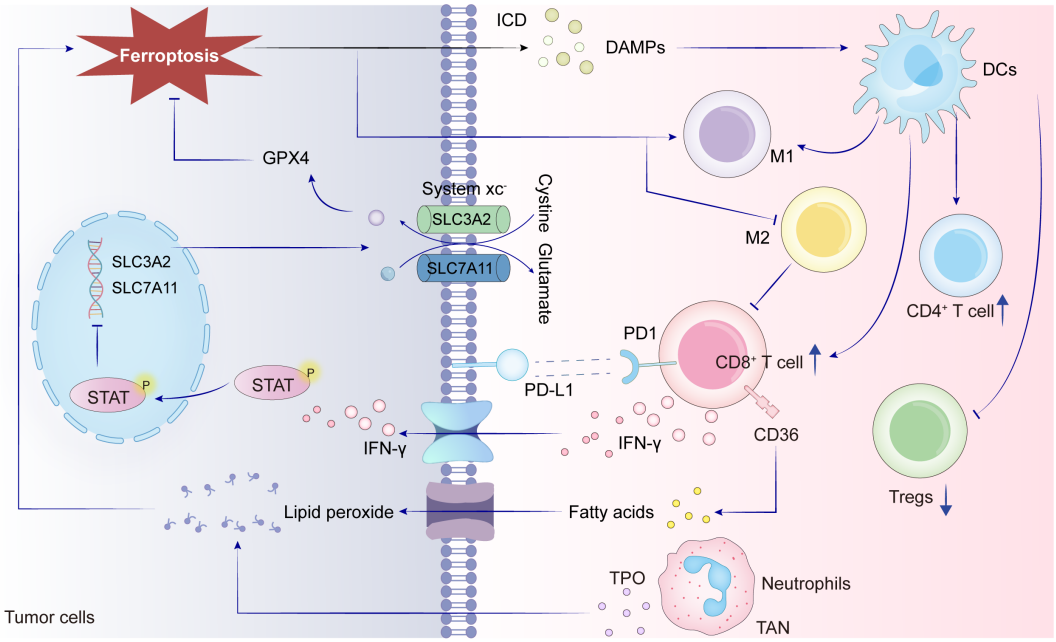

Figure 4: Ferroptosis in Tumor Immunity. Ferroptosis enhances the release of HMGB1 and ATP from tumor cells, boosting proliferation, activation, and immunogenicity of dendritic cells (DCs). Activated CD8⁺ T cells secrete IFN-γ, which downregulates the expression of system Xc- subunits SLC3A2 and SLC7A11 in cancer cells, increases lipid peroxidation, and heightens sensitivity to ferroptosis. Increased expression of CD36 on tumor-infiltrating CD8⁺ T cells promotes fatty acid uptake via a CD36-dependent pathway, leading to accumulation of intracellular lipid peroxides and promoting ferroptosis. Ferroptotic tumor cells induce M1 polarization of macrophages, releasing TNF to enhance inflammation and immune response. Tumor-associated neutrophils (TANs) transfer granules containing peroxidases to tumor cells, causing accumulation of iron-dependent lipid peroxides and inducing ferroptosis.

and RSL3, promotes the release of HMGB1 from tumor cells in an autophagy-dependent manner. This interaction with the receptor for advanced glycation end-products (RAGE) induces M1 polarization of macrophages and the release of TNF, which stimulates inflammation and immune responses.[191] However, tumor cells undergoing ferroptosis can release proteins coded by the K-RasG12D gene, which are taken up by macrophages through the RAGE pathway, promoting M2 polarization *via* a STAT3-dependent fatty acid oxidation pathway.[192] Balancing the dosage of ferroptosis inducers to maximize tumor cell killing while minimizing M2 polarization of macrophages is a critical issue that needs to be addressed.

Similar to other immune cells, the sensitivity of neutrophils to ferroptosis is influenced by the expression of GPX4. Pathologically activated neutrophils-myeloid-derived suppressor cells (PMN-MDSCs) exhibit immunosuppressive functions. Downregulation of GPX4 promotes ferroptosis in PMN-MDSCs. Compared to PMN-MDSCs isolated from bone marrow and spleen, tumor-associated PMN-MDSCs are more susceptible to ferroptosis, which can mediate immunosuppression following their ferroptotic death.[193] Neutrophils can also induce ferroptosis in tumor cells. Although multiple studies indicate that tumor-associated neutrophils (TANs) can facilitate tumor progression, in glioblastoma, TANs transfer granules containing myeloperoxidase to tumor cells. This transfer leads to the accumulation of lipid peroxides dependent on iron ions within the tumor cells, thereby inducing ferroptosis (Figure 4).[194]

Cuproptosis in anti-tumor immunity

Cuproptosis has been identified as a potent trigger for ICD. Recent studies have elucidated the role of cuproptosis in eliciting immune responses within the TME. During cuproptosis, the damage to tumor cell membranes results in the release of various DAMPs such as ATP, HMGB1, and calreticulin (CRT). These molecules enhance the maturation of DCs and activation of $CD8^+$ effector T cells, ultimately triggering a sustained anti-tumor immune response.[195–198]

Cuproptosis has been demonstrated to reshape tumor immunity within the microenvironment of clear cell renal cell carcinoma (ccRCC) by activating the tumor antigen presentation process through the cGAS-STING signaling pathway.[199] The cGAS-STING pathway plays a pivotal role in innate immune signaling, engaging DNA to trigger various immune responses. This includes the upregulation of IFN, pro-inflammatory cytokines, and chemokines through IRF3 and NF-κB, enhancing the cytolytic activity of NK cells and fostering the expansion of cytotoxic $CD8^+$ T cells.[200] In DCs co-cultured with cuproptosis inducers

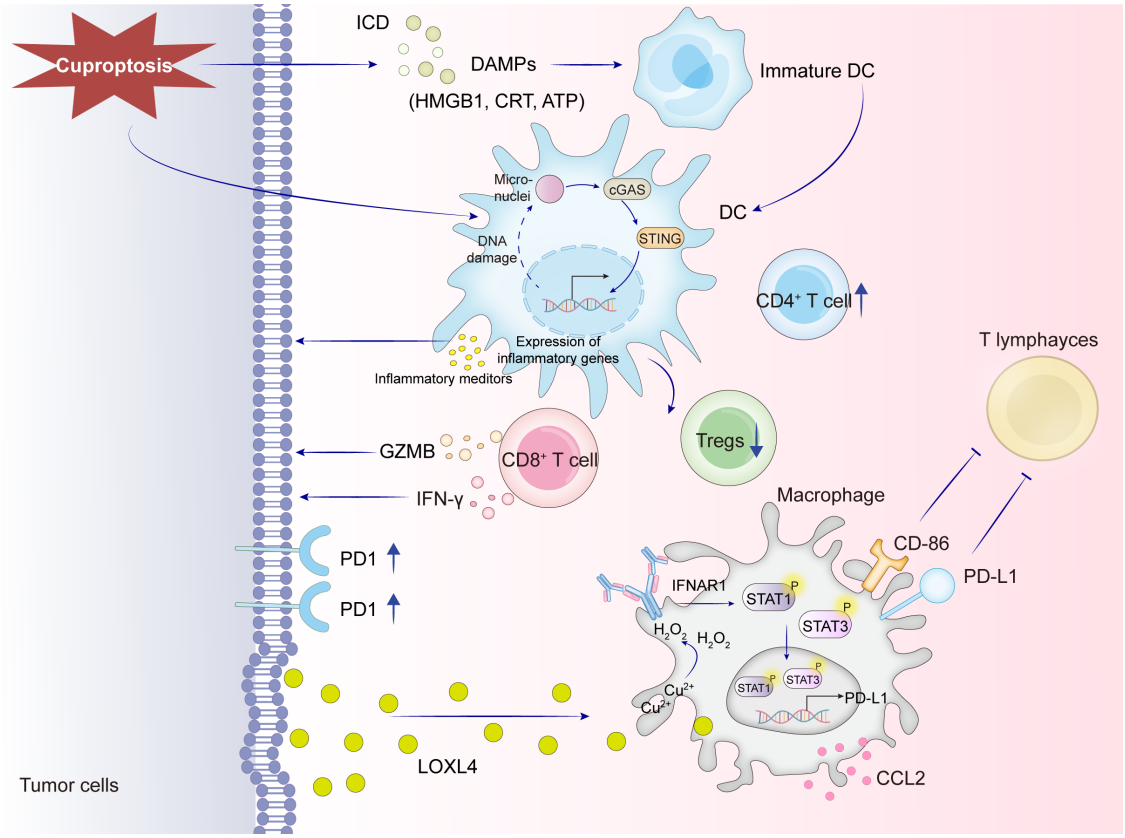

Figure 5: Cuproptosis in Tumor Immunity. Tumor cells undergoing cuproptosis release various DAMPs (such as ATP, HMGB1, and CRT), which promote the maturation of dendritic cells (DCs) and the activation of CD8⁺ effector T cells. Cuproptosis enhances antitumor immunity by modulating the cGAS-STING signaling pathway. This pathway is activated in dendritic cells by tumor cells experiencing cuproptosis, subsequently promoting the release of inflammatory mediators. Tumor cells also release lysyl oxidase-like 4 (LOXL4), which, when encountered by macrophages *ex vivo*, induces an immunosuppressive phenotype and activates the expression of programmed death-ligand 1 (PD-L1), further inhibiting the function of CD8⁺ T cells.

(Elesclomol and CuCl2), the cGAS-STING activity increased in a dose-dependent manner, with increased intracellular cGMP activity, and elevated levels of IL-2, TNF-α, IFN-γ, and CXCL10/11 in the culture supernatant. In tumor-bearing mice, combining cuproptosis inducers with anti-PD-1 therapy synergistically enhances the levels of circulating $CD45^+CD8^+$ T cells.[199]

Copper levels within tumors influence the expression of PD-L1 in tumor cells and regulate immune evasion triggered by PD-L1.[201] Conversely, copper chelators, such as DC or TEPA, attenuate the phosphorylation of STAT3 and EGFR, which leads to ubiquitin-mediated degradation of PD-L1. Furthermore, copper chelators can also enhance the infiltration of $CD8^+$ T cells and NK cells, thereby inhibiting tumor growth.[201] Lysyl oxidase-like 4 (LOXL4) is an amine oxidase that, in a copper-dependent manner, catalyzes the conversion of amines, generating hydrogen peroxide (H2O2) and ammonia as byproducts. LOXL4 exerts immunosuppressive effects on macrophages predominantly through disrupting IFN-mediated signaling pathways and transcription-dependent activation of PD-L1. The action of hydrogen peroxide scavengers or copper chelation through LOXL4 effectively eliminates IFN-induced PD-L1 expression (Figure 5). [202]

It is noteworthy that the combination of the copper ion carrier Disulfiram (DSF) with copper (DSF/Cu) has been demonstrated to exert robust anti-tumor effects. Treatment with DSF/Cu promotes the activation and maturation of DCs, and when used in conjunction with CD47 blocking agents, further enhances DC maturation, subsequently increasing the cytotoxic activity of $CD8^+$ T cells. Mechanistically, DSF/Cu facilitates the nuclear accumulation and aggregation of Nuclear Protein Localization protein 4 (NPL4), thereby inhibiting the ubiquitin-proteasome system and inducing ER stress.[203] The inhibition of NPL4 induced ICD-associated damage-associated molecular patterns.

RCD and pro-tumor immunity

Based on the aforementioned studies, necroptosis, pyroptosis, ferroptosis, and cuproptosis have been shown to enhance immune responses against tumors.

However, research indicates that these forms of RCD also influence the survival, proliferation, differentiation, and activation of immunosuppressive cells, including Tregs, M2 macrophages, and myeloid-derived suppressor cells (MDSCs). Additionally, immune-promoting cells may also be negatively regulated by various forms of RCD. Furthermore, during ICD, the release of DAMPs not only stimulates anti-tumor immune responses but may also promote the development of inflammatory responses that favor tumor growth. For example, RIPK3-dependent necroptosis in pancreatic cancer cells enhances the expression of sin3A-associated protein 130 (SAP130) and the release of chemokines such as CXCL1 and CXCL5,[204,205] leading to the recruitment of immunosuppressive cells like MDSCs, fostering an immunosuppressive TME that facilitates cancer cell migration and invasion. Additionally, DAMPs released from cells undergoing pyroptosis recruit inflammatory cells and stimulate the release of regulatory cytokines, such as IL-18, IL-1β, and IL-10.[206–209] These cytokines contribute to angiogenesis, tumor cell proliferation, and metastasis, thereby promoting inflammation and tumor progression.[210,211] Additionally, iron-dependent cancer cells, in the absence of GPX4, activate the STING-dependent DNA sensing pathway in macrophages by releasing 8-hydroxyguanosine (8-OHG),[212] promoting the release of cytokines such as IL-6 and nitric oxide synthase 2 (NOS2), thereby fostering an inflammatory milieu conducive to pancreatic cancer.[212] As triggers of ferroptosis, ROS can also suppress immune responses by inhibiting the formation of TCR and MHC antigen complexes within T cells.[213,214] Therefore, these studies indicate that when employing RCD in targeted cancer therapies, we must also consider its potential effects on promoting tumor immunity. We recommend readers consult a recent comprehensive review for a detailed discussion of the pro-tumorigenic immune effects of RCD.[29]

ANTICANCER DRUGS TARGETING RCD

Cancer immunotherapy based on RCD represents a promising and continually evolving approach to cancer treatment. Tumor cells and other cells within the TME undergo apoptosis, pyroptosis, necroptosis, ferroptosis, and cuproptosis, which may contribute to enhanced antitumor immunity. Inducing ICD has been shown to be effective in many drugs approved for anticancer therapy.[215] This review encompasses FDA-approved anticancer drugs that target a range of newly identified mechanisms of cell death, which demonstrate considerable potential to enhance anti-tumor immunity (Table 1).

Apoptosis is a highly regulated form of cell death. The BCL-2 gene family plays a central role in regulating PCD by controlling pro-apoptotic and anti-apoptotic intracellular signaling pathways.[216] The selective inhibition of specific anti-apoptotic BCL 2 family proteins has demonstrated efficacy as a treatment for cancer.[216] Recent studies have also found that the BCL-2 inhibitor venetoclax enhances CART cell immunotherapy.[217] Navitoclax, a second-generation BH3 mimetic and dual antagonist of BCL-2 and BCL-XL, exhibits synergistic effects when combined with the BAX activator BTSA1.2 in apoptosis-resistant cancer cells, xenografts, and patient-derived tumors.[218] The BCL2 inhibitor venetoclax, either alone or in combination with PD-1 blockade, enhances DC antigen presentation and activation, thereby inhibiting tumor immune surveillance *via* DC-specific immune checkpoints.[219] Additionally, the DNA methyltransferase (DNMT) inhibitor decitabine has been found to induce mitochondrial alterations (such as Bak activation, loss of transmembrane potential, and reactive oxygen species production) in p53 mutant leukemia T cells, thereby activating the intrinsic apoptotic pathway.[220] Furthermore, the level of GSH and activity of GPX4 in MDS cells are decreased by decitabine, leading to ferroptosis caused by heightened ROS levels.[221] Moreover, decitabine enhances and sustains the anti-tumor potential of CAR T cells through epigenetic reprogramming, synergizing with immunotherapy.[222]

The necroptosis found in infections and sterile inflammation also plays a huge role in cancer therapy. Fingolimod, the sphingosine analog FTY720, targets I2PP2A/ SET to inhibit lung tumor growth through RIPK1 kinase structural domain mediated PP2A activation and induce necroptosis.[223] Notably, fingolimod has been found to limit the number of tumor-infiltrating lymphocytes (TILs) in solid tumors, thus potentially inhibiting antitumor immune responses.[224] The novel pan-caspase inhibitor IDN-7314 promotes 5- fu-induced TNF-α-dependent necroptosis driven by RIP1 kinase and NF-κB to inhibit tumor growth.[225] As a commonly used agent in colorectal cancer (CRC) treatment, it also has a good synergistic effect with PD-L1 monoclonal antibody.[226] Chloroquine (CQ) has been demonstrated to upregulate cellular endogenous RIPK3-induced CRC necroptosis.[227] Studies have demonstrated that CQ blocks immune escape and improves the efficacy of antitumor immunotherapy.[228] Artesunate, a widely used antimalarial drug, induces necroptosis and ferroptosis in tumor cells.[229] Artesunate effectively reduces TAZ and PD-L1 expression in non-small cell lung cancer (NSCLC) promotes antitumor immunotherapy in NSCLC antitumor immunity and overcomes epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) resistance.[230]

Pyroptosis-based interventions combined with tumor immunotherapy can significantly improve cancer control. Simvastatin activates the NLRP3 inflammasome and

Table 1: Summary of clinically approved drugs that may induce ferroptosis, necroptosis, and pyroptosis in cancers and their effects on antitumor immunity

Drug Name	General Usage	Target	Effect on Tumor RCD	Effect on Antitumor Immunity
Navitoclax	Anticancer drug	BCL-2/BCL-XL	Apoptosis induction[269]	Enhanced antitumor immunity[219]
Venetoclax	Anticancer drug	BCL-2	Apoptosis induction[270]	Enhanced antitumor immunity[271]
LCL161	Anticancer drug	IAP	Apoptosis induction[272, 273]	Enhanced antitumor immunity[274]
Decitabine	Anticancer drug	GPX4	Apoptosis/Ferroptosis induction[221,275]	Enhanced antitumor immunity[222]
FTY720	Multiple sclerosis	RIPK1	Necroptosis induction[223]	Increased immune suppression[276,277]
Chloroquine (CQ)	Antimalarial drug	RIPK3	Necroptosis induction[227]	Enhanced antitumor immunity[228]
5-fluorouracil (5-FU)	Anticancer drug	TNF-α/RIPK3	Necroptosis/pyroptosis induction[225,278]	Enhanced antitumor immunity[279]
Sorafenib	Anticancer drug	System Xc-	Necroptosis/ferroptosis induction[280,281]	Increased immune suppression[282]
Artesunate	Antimalarial drug	ROS	Necroptosis/ferroptosis induction[283,284]	Increased immune suppression[230]
Resibufogenin	Heart failure drug	RIPK3, MLKL	Necroptosis/pyroptosis/ ferroptosis induction[285–287]	Unknown
Simvastatin	Hyperlipemia drug	Casepase1	Pyroptosis induction[231]	Enhanced antitumor immunity[232]
Doxorubicin	Anticancer drug	DFNA5	Pyroptosis induction[288]	Enhanced antitumor immunity[289]
Iron	Nutrient	Ferritin/GSDME	Pyroptosis induction[243]	Enhanced antitumor immunity[290]
Metformin	Anti-diabetes drug	GSDMD	Pyroptosis induction[240]	Enhanced antitumor immunity[241]
Drug Name	General Usage	Target	Effect on Tumor RCD	Effect on Antitumor Immunity
Docosahexaenoic acid (DHA)	Nutrient	GSDMD	Pyroptosis induction[291]	Enhanced antitumor immunity[258]
Paclitaxel (PTX)	Anticancer drug	GSDMD	Pyroptosis induction[278]	Enhanced antitumor immunity[292]
BRAF and MEK Inhibitor	Anticancer drug	GSDMD	Pyroptosis induction[173]	Enhanced antitumor immunity[173]
Cisplatin	Anticancer drug	GSH/GSDME	Pyroptosis induction[293]	Enhanced antitumor immunity[294]
Doxorubicin	Anticancer drug	GSH/GSDME	Pyroptosis induction[295]	Unknown
Anthocyanin	Nutrient	NLRP3	Pyroptosis induction[296]	Enhanced antitumor immunity[297]
Lapatinib	Anticancer drug	Ferritin	Ferroptosis induction[244]	Unknown
Neratinib	Anticancer drug	Ferritin	Ferroptosis induction[298]	Enhanced antitumor immunity[299]
Etoposide	Anticancer drug	GPX4	Ferroptosis induction[300]	Unknown
Dihydroartemisinin	Antimalarial drug	GPX4	Ferroptosis induction[301]	Enhanced antitumor immunity[302]
Apatinib	Anticancer drug	GPX4/System Xc-/Nrf2	Ferroptosis induction[247]	Enhanced antitumor immunity[303]
Trigonelline	Nutrient additive	Nrf2	Ferroptosis induction[283]	Enhanced antitumor immunity[304]
Sulfasalazine	Anti-inflammatory drug	System Xc-	Ferroptosis induction[281]	Unknown
Glutamate	Nutrient	System Xc-	Ferroptosis induction[94]	Increased immune suppression[305]
Sulfasalazine	Anti-inflammatory drug	System Xc-	Ferroptosis induction[306]	Synergistic immunotherapy[254]

Table 2: Summary of the nano compounds that target cuproptosis mechanisms for synergistic immunotherapy

Agent Name	Content	Effect on Tumor RCD	Cancer Type	Effects on Antitumor Immunity	References
NP@ESCu	Co-encapsulate elesclomol (ES) and Cu to form nanoparticles	Cuproptosis induction	Subcutaneous bladder cancer	Enhanced antitumor immune	[307]
LCP NPs	pH-responsive lipid-coated calcium phosphate nanoparticles co-loaded with Cu and DSF	Cuproptosis induction	Colon carcinoma	Enhanced antitumor immune	[308]
CuCHNCs	Peroxidase-like biomineralized copper (II) carbonate hydroxide nanocrystals inside single albumin nanocages	Cuproptosis induction	Triple-negative breast cancers	Enhanced antitumor immune	[309]
CuX-P	DSF/Cu^{2+}	Cuproptosis induction	Triple-negative breast cancers	Enhanced antitumor immune	[265]
CQG NPs	Self-destructive and multi-enzymatically active copper-quinoneGOx nanoparticles	Pyroptosis and cuproptosis induction	Triple-negative breast cancers	Enhanced antitumor immune	[197]

caspase-1, leading to GSDMD-dependent pyroptosis and inhibiting the proliferation and migration of NSCLC cells through typical pathways.[231] An individual intraosseous dose of simvastatin inhibited the development of breast cancer by activating $CD8^+$ T cells and reducing the expression of PD-1, TIM3, and CTLA4.[232] The chemotherapeutic agent's doxorubicin, paclitaxel, and cisplatin-induced pyroptosis in particular cancer cells expressing GSDME.[86,233] It is noteworthy that cytoprotective mitochondrial autophagy, dependent on the ROS/HO-1/GPX4 axis, eased cisplatin-induced nephrotoxicity caused by ferroptosis in renal tubular epithelial cells.[234] Furthermore, doxorubicin has been demonstrated to trigger ICD in hepatocellular carcinoma (HCC).[235] Paclitaxel promotes immune cell death in metastatic triple-negative breast cancer and modulates the tumor microenvironment.[236,237] Cisplatin increases the expression of PD-L1, enhancing immune checkpoint blockade therapy in non-small cell lung cancer.[238] Additionally, metformin activates the AMPK/SIRT1/NF-κB pathway, inducing mitochondrial dysfunction and triggering caspase3 activation and GSDME-N production, leading to cellular pyroptosis that inhibits cancer cell proliferation.[239] Additionally, metformin targets the miR-497/PELP1 axis to induce GSDMD-dependent cell death in oesophageal squamous cell carcinoma.[240] Moreover, metformin enhances antitumor immunity by decreasing the stability and membrane localization of PD-L1.[241] Iron can participate in the Fenton reaction, generating ROS, which induces lipid peroxidation and leads to ferroptosis.[242] Additionally, iron initiates GSDME-dependent pyroptosis *via* the ROS signaling pathway.[243] Breast cancer cells experienced ferroptosis induced by tyrosine kinase inhibitors lapatinib and neratinib through the inhibition of ferritin transport.[244,245] Neratinib, in combination with histone deacetylase inhibitors (HDAC) , has been found to enhance the effectiveness of anti-PD-1 therapy *in vivo*.[246] Additionally, apatinib has been shown to induce ferroptosis through lipid peroxidation and to support immune recovery post-radical mastectomy.[247,248]

Ferroptosis in tumors can enhance cancer immunity and immunotherapy. Sorafenib is a widely used treatment for HCC and induces ferroptosis by reducing GSH synthesis through inhibiting system Xc-.[249,250] The use of the iron chelator, deferasirox, results in the transition from sorafenib-induced cell death to apoptosis and necroptosis.[251] Sorafenib is known to promote the secretion of IL-12 in TAM and the resultant apoptosis of cancer cells using sub-therapeutic doses, which combine with mCAR T cell production for antitumor effects.[252] Furthermore, sorafenib and sulphasalazine act synergistically to induce ferroptosis in HCC cells.[253] Sulphasalazine enhances antitumor immune responses when synergized with radiotherapy.[254] Altretamine, an ovarian cancer treatment commonly used, has been discovered to have a comparable effect to sulphasalazine by targeting GPX4 and inducing ferroptosis.[255] Etoposide, a phenolic antitumor medication, effectively exhausts GSH from myeloid leukemia cells resulting in ferroptosis. Further investigation is needed to understand the association between etoposide and tumor immunity.[256] Dihydroartemisinin (DHA), a drug used to treat malaria, reduces cancer cell viability and proliferation.[5] DHA in combination with cisplatin induces ferroptosis and inhibits pancreatic ductal adenocarcinoma by promoting GPX4 degradation, ROS production, and NCOA4-mediated ferritin degradation.[257] DHA has been shown to decrease PD-L1 protein expression, thereby inhibiting immune escape from colorectal cancer cells.[258] Statins have been shown to cause depletion of isopentenyl pyrophosphate, leading to GPX4 downregulation, similar to the mechanism of GPX4 inhibitors, which leads to ferroptosis.[259,260] In addition, statins play a role in the regulation of antitumor immune responses in tumors.[261]

Initially, it was believed that elesclomol triggered a rise in ROS within cancer cells, leading to apoptosis. Presently, it has been discovered that elesclomol acts as a copper ionophore to induce cuproptosis and synergizes with immune checkpoints to inhibit cancer. In recent investigations, tiny molecule compounds that target cuproptosis have shown significant potential for treating cancer. In Table 2, we present a summary of the nanocompounds that target cuproptosis mechanisms for synergistic immunotherapy and have been tested *in vivo* and/or *in vitro*, demonstrating promising results.

CONCLUSION AND PERSPECTIVES

Substantial research has focused on targeting various forms of RCD for cancer therapy, with tumor immunotherapy emerging as a field with significant potential.[1,5] However, ICIs remain ineffective for many cancer patients. Our findings indicate that RCD not only initiates an immune response but also enhances lymphocyte infiltration and improves tumor responses to immunotherapy. Thus, inducing RCD in tumor cells represents a promising strategy for cancer treatment.[8] The review synthesizes evidence on five RCD pathways and their links to antitumor immunity, discussing FDA-approved drugs that target RCD and their synergistic effects with tumor immune responses. Currently, there are no FDA-approved drugs specifically for cuproptosis. Nevertheless, several innovative small molecules and nanomaterials have demonstrated potential in inducing cuproptosis and enhancing antitumor immunity.[262–266]

In addition to the discovery of cuproptosis in 2022, a new type of cell death called disulfidptosis has been identified, indicating that our understanding of RCD is still evolving.[116,267] The development of drugs that target this novel form of cell death represents a valuable area of research. Designing drugs or small molecules that effectively target RCD to treat cancer while passing safety tests poses significant challenges. Our review suggests that screening FDA-approved drugs with these effects from established libraries and applying them to new disease contexts could be a promising direction. Furthermore, we have proposed that drugs such as fingolimod, which induces both necroptosis and ferroptosis by targeting RIPK1 and glutamate,[223,268] may increase immunosuppression, and suggest that studies of RCD-inducing drugs need to precisely identify their different effects on antitumor immunity.

In conclusion, our review suggests a new direction for tumor treatment. We advocate for the investigation of targeted cell death drugs, the exploration of their immune interactions with tumors, and the development of new mechanisms for cancer treatment using FDA-approved drugs, extending from classical RCD, such as apoptosis, to novel forms of cell death. Future studies utilizing animal models are encouraged to uncover additional outcomes. Furthermore, additional clinical trials are planned to investigate new cell death modulators in cancer patients.

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Author Contributions

ZG and YL wrote the original draft and visualization and participated in conceptualization. DC, DL, YM, and QZ conceptualized, reviewed, and revised the manuscript, and participated in visualization. FZ, GD, and XC led validation and funding acquisition and participated in review and editing. YS, GD, and XC dominated supervision and project administration and participated in conceptualization.

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Ethical Approval

Not applicable.

Informed Consent

Not applicable.

Conflict of Interest

The authors have stated that they have no conflicts of interest.

Use of Large Language Models, AI and Machine Learning Tools

None declared.

Data Availability Statement

No additional data is available.

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