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Programmed Cell Death in Cancer

Yuang Wei[1,2,3,4] | William Hankey[5] | Dongliang Xu[2,3,4] | Fuwen Yuan[1]

[1]Cancer Research Center, School of Integrative Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China | [2]Urology Centre, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China | [3]Surgical Institute of Integrative Medicine, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China | [4]Shanghai Key Laboratory of Traditional Chinese Clinical Medicine, Shanghai, China | [5]Department of Genetics, The University of North Carolina At Chapel Hill, Chapel Hill, North Carolina, USA

Correspondence: Dongliang Xu (dr_xudongliang@shutcm.edu.cn) | Fuwen Yuan (yuanfuwen@pku.edu.cn)

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ABSTRACT

Cancer remains the most lethal disease globally, despite the significant progress made in early screening, surgery, and therapeutic development in recent decades. Programmed cell death (PCD) is a genetically regulated process essential for eliminating aberrant cells, yet its dysregulation drives tumorigenesis and therapy resistance. In this review, we present a complete discovery timeline of them and comprehensively synthesize the roles and mechanisms of major PCD forms, such as apoptosis, necroptosis, autophagy, pyroptosis, ferroptosis, and cuproptosis, across diverse cancer types. We not only detail the molecular mechanisms, dual functions, and alterations of these PCD modalities in cancers, but also summarize their interconnections and intrinsic crosstalk. Furthermore, we comprehensively discuss how diverse therapies, including chemotherapy, radiotherapy, immunotherapy, targeted agents, and hormone therapy, engage and manipulate specific PCD pathways, revealing the involvement of PCD in cancer treatment mechanisms. This review integrates extensive preclinical and clinical evidence on PCD-targeted therapies with an in-depth focus on ferroptosis, including its regulatory networks and therapeutic relevance. Special emphasis is placed on prostate cancer, highlighting the PCD-based translational opportunities in this common malignancy. Taken together, we provide novel insights into the complex interplay between PCD and cancer biology and offer a framework for developing precision oncology therapies.

1 | Introduction

Cell death is categorized into accidental and programmed forms. Accidental death results from physical, chemical, or mechanical disruptions, while programmed cell death (PCD) is a genetically regulated process triggered under specific cellular conditions [1]. The 2018 update by the Nomenclature Committee on Cell Death classified 12 distinct PCD mechanisms, ranging from classical apoptosis and pyroptosis to newer forms like ferroptosis. Each subtype is characterized by unique biochemical signatures and physiological implications, offering nuanced insights into disease pathogenesis and therapy [2].

With the deepening understanding of the regulatory mechanisms underlying cell death, emerging PCD modalities have been progressively studied, such as copper (Cu) overload-induced cuproptosis [3], sodium-associated necrotic cell death under sodium overload [4], and disulfide stress-triggered disulfidptosis [5]. These emerging pathways underscore the complexity of intracellular stress responses and highlight previously unrecognized

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links between metal ion homeostasis, metabolic stress, and cell viability. As a result, the study of PCD has evolved into a central pillar of biomedical research, with direct relevance to cancer biology, immunology, and precision medicine.

The dysregulation of PCD is now recognized as a hallmark of cancer and other pathological states. In oncology, PCD exhibits a dual character: while it suppresses tumor development by eliminating unstable cells, many tumors manipulate these pathways to form immune evasion and facilitate metastasis and therapeutic resistance [6]. Pan-cancer analyses have revealed recurrent mutations and expression patterns in PCD-related genes, with significant correlations to prognosis and treatment responses. These findings have prompted the development of targeted therapies aimed at modulating cell death pathways to improve clinical outcomes [7, 8].

Leveraging PCD has become a therapeutic strategy in cancers, and treatment approaches have progressively shifted from isolated pathway modulation toward integrated strategies. For example, the activation of PANoptosis, a form of PCD which combines apoptosis, necroptosis, and pyroptosis via the assembly of their core components into a multiprotein complex known as the PANoptosome, represents a promising multitargeted strategy for cancer therapy. Emerging studies suggest this may be more immunogenic and effective at overcoming resistance mechanisms [9–12]. Therapies designed to activate PANoptosis have shown potential in preclinical models and are under exploration for refractory tumors such as triple-negative breast cancer (TNBC), a refractory subtype of breast cancer (BCa) that lacks expression of estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 (HER2) [13, 14]. In recent years, ferroptosis, due to its dependence on iron (Fe) metabolism and lipid peroxidation, has gained attention for its capacity to reshape the tumor microenvironment (TME) and enhance responses to immunotherapy [15–17]. Besides, clinical translation has witnessed breakthroughs of multimodal strategies based on PCD-targeted treatment. A hallmark example of successful clinical translation is the approval of programmed cell death protein 1/ligand 1 (PD-1/PD-L1) immune checkpoint inhibitors (ICIs), such as pembrolizumab and nivolumab [18]. These therapies reactivate cytotoxic T lymphocytes and restore apoptosis in tumor cells, demonstrating clinical benefits across various cancers and have become standard-of-care treatments in multiple oncologic guidelines [19]. Additionally, ferroptosis inducers are moving toward clinical application, offering promise for overcoming apoptosis resistance in refractory cancers [19]. These therapies offer an avenue to overcome resistance to apoptotic cell death in tumors.

Despite these advances, several challenges remain. The mechanisms of PCD resistance in therapy-resistant tumors are not fully understood, and the complex interplay between PCD types within the TME demands deeper investigation [20]. This review is structured to first examine the molecular underpinnings and classification of PCD, then transition into its role in cancer development and therapy, following a discussion on translational challenges and future research directions. We aim to synthesize current insights from pan-cancer analyses on PCD, spotlight emerging therapeutic strategies, especially ferroptosis and prostate cancer (PCa), and provide a comprehensive theoretical framework for advancing precision oncology.

2 | Roles of PCD in Cancers

Many subtypes of PCD have been well documented in the pathogenesis and treatment of cancers. In addition to the best-known forms of PCD like apoptosis, autophagy, necroptosis, pyroptosis, and ferroptosis [21, 22], studies are increasingly uncovering the involvement of other types of PCD in cancers [23], including entosis [24], pyroptosis [25], parthanatos [26], and the newly identified cuproptosis and disulfidptosis [27, 28] (Figure 1). In this section, we will provide an overview of the recent updates on major PCD types and the molecular networks involved in cancer progression and treatment.

2.1 | Apoptosis: The Fundamental Programmed Cell Death

Apoptosis, the first formally recognized form of PCD in mammalian cells, is a tightly regulated and evolutionarily conserved process crucial for maintaining cellular homeostasis. The term “apoptosis” was introduced in 1972 by Kerr, Wyllie, and Currie, drawing inspiration from James Cormack at the University of Aberdeen [29]. Morphologically, apoptosis is characterized by distinctive features such as cytoplasmic shrinkage, chromatin condensation, and the formation of apoptotic bodies, phenomena observed across both physiological and pathological conditions [30]. Mechanistically, apoptosis is broadly categorized into two pathways: the intrinsic (mitochondrial) and extrinsic (death receptor-mediated) pathways, each governed by distinct molecular triggers and signaling cascades. The intrinsic pathway is typically initiated by intracellular stress signals, including DNA damage, cellular stress, and mitochondrial dysfunction. It is primarily regulated by the B cell lymphoma-2 (BCL-2) family, which contains antiapoptotic proteins (e.g., BCL-2, BCL-XL, and A1/BFL1), proapoptotic BCL-2 homology region 3 (BH3)-only proteins (e.g., BIM, BID, and NOXA), and proapoptotic effectors such as BCL-2-associated X (BAX), BCL-2 antagonist/killer 1, and BCL-2-related ovarian killer. Upon activation, these effectors mediate mitochondrial outer membrane permeabilization (MOMP), leading to cytochrome c release and the activation of caspase-9, which in turn triggers the downstream effector caspases, such as caspase-3 and caspase-7, culminating in cell death [9]. The extrinsic pathway, on the other hand, is initiated by the engagement of membrane-bound death receptors, such as Fas (CD95), tumor necrosis factor receptor 1 (TNFR1), and TRAIL receptors (DR4 and DR5). These receptors possess a cytoplasmic death domain (DD) that enables the recruitment of adaptor proteins. For instance, upon binding of Fas ligand (FasL) secreted by activated T cells to Fas, the adaptor protein Fas - associated DD (FADD) is recruited, which subsequently activates initiator caspase-8. This leads to a caspase cascade that converges on effector caspases, executing apoptosis in a controlled and immunologically silent manner [6].

In the context of diseases, Kerr and Searle [31] first observed a pronounced epithelial cell loss in the prostates of castrated

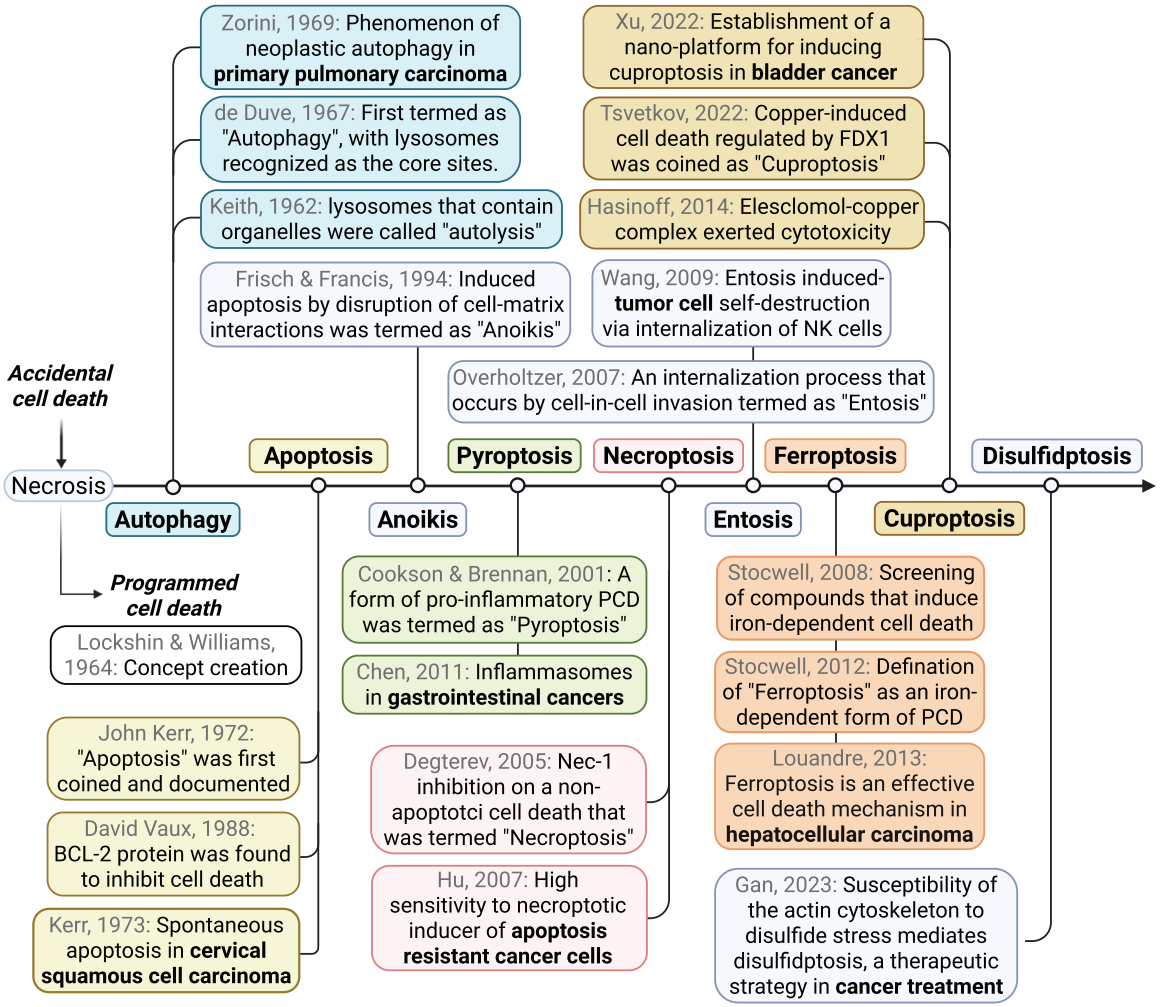


FIGURE 1 | The milestones of major PCDs and their pioneering studies in cancers. The classification of cell death underwent a paradigm shift in the 1960s, transitioning from the traditional view of accidental cell death (necrosis) to the recognition of regulated physiological cell death mechanisms. We outlined the landmark events of major PCDs using different colors, including the proposal of their concepts, the discoverers, and the first research reported in cancer.

rats, an effect attributed to heightened apoptotic activity, which was mitigated by exogenous testosterone administration, thereby preserving cell integrity postcastration. At the same time, they first reported the spontaneous apoptosis in squamous carcinomas of the uterine cervix [32]. The research interest in apoptosis in cancer experienced a significant surge starting after the 1990s. The BCL-2 family, with its pro- and antiapoptotic constituents, is implicated in the delicate balance of cell survival signaling, often perturbed in cancers through the overexpression of antiapoptotic proteins, fostering a survival bias and impeding therapeutic efficacy. Elevated BCL-2 expression has been correlated with poor prognosis and resistance to hormone therapy, targeted agents, or cytotoxic chemotherapy across a broad spectrum of malignancies, such as lymphomas, BCa, and non-small cell lung cancer [33–35]. Recent studies have further emphasized that restoration of PTEN function combined with radiotherapy (RT), as well as dual inhibition of the PI3K/Akt signaling axis and antiapoptotic BCL-XL in PTEN-deficient tumors, can effectively overcome BCL-2-mediated survival advantages, highlighting the multifaceted regulation of apoptotic pathways in diverse cancer contexts [36–38]. High-grade intraepithelial neoplasia is recognized as a critical precursor in the neoplastic development of vaginal, anal, cervical, pancreatic, colorectal, gastric, and prostatic cancers, characterized by cell proliferation and an augmented proliferation index [39]. The aberrant accumulation of these neoplastic cells suggests a disruption in the regulatory pathways governing cell proliferation and death [40]. Johnson et al. [41] have demonstrated that BCL-2 expression is significantly upregulated in high-grade prostatic intraepithelial neoplasia, compared with PCa and benign prostatic epithelium, suggesting an early involvement of apoptotic dysregulation in PCa pathogenesis. Further studies have corroborated these findings, with BCL-2 expression detectable across multiple cellular hierarchies in diverse tumor precursor lesions. Pronounced immunoreactivity has been observed in subsets of ductal carcinoma in situ of the esophageal, anal, and prostatic metaplasia [42–44]. These observations collectively underscore the pivotal role of apoptotic dysregulation in the early stages of tumorigenesis across a broad spectrum of cancers.

Moreover, the proapoptotic effector BAX constitutes a critical control point in the intrinsic death pathway and has emerged as

a promising therapeutic target in treatment-refractory malignancies [45]. Phytochemicals such as apigenin and quercetin have been shown to shift the balance toward apoptosis by downregulating antiapoptotic BCL-2 family members and upregulating BAX in diverse cancer cell models, such as breast and PCa cell lines [46–48]. The extrinsic apoptosis cascade, triggered by death ligands such as TRAIL and FASL, likewise plays a central role in tumor immunosurveillance and has been exploited genetically and pharmacologically across multiple cancer types [49]. Immunotherapies leveraging TRAIL/FASL signaling have demonstrated potent induction of apoptosis in solid tumors [50–52]. Collectively, these findings illustrate the molecular networks of intrinsic and extrinsic apoptotic pathways contributing to oncogenesis, tumor progression, and therapy resistance across a broad spectrum of cancers, and underscore apoptosis as a readily targetable mechanism in current and emerging cancer therapies.

2.2 | Necroptosis: A Form of Programmed Necrosis

Necroptosis, a form of programmed necrosis distinct from apoptosis, was first characterized by Degterev et al. [53]. It is characterized by morphological features such as cell and organelle swelling, loss of membrane integrity, production of reactive oxygen species, and the release of apoptosis-inducing factor (AIF), which do not occur in necrosis [54]. Necroptosis can be initiated in response to a range of stimuli, including death receptor signaling, pathogen invasion, and various forms of cellular stress. Notably, stimulation of death receptors such as TNFR1, Fas, DR4, and DR5 can lead to necroptosis under conditions where caspase-8 is inhibited or absent. Under normal circumstances, caspase-8 prevents necroptosis by cleaving receptor-interacting protein kinase 1 (RIPK1). However, when caspase-8 is inactive, RIPK1 becomes stabilized and can initiate downstream signaling independent of caspase activity. The identification of small molecule inhibitors like necrostatin-1 (Nec-1), which selectively inhibits RIPK1, has been instrumental in delineating necroptosis from other forms of cell death [55]. In a canonical RIPK1-dependent necroptosis pathway, the activation of TNF leads to the assembly of a transient intracellular complex known as complex I, which is formed through the interaction of the TNFR1 DD with various proteins. This complex recruits several key proteins, including the adaptor protein TNF receptor-associated DD (TRADD), RIPK1, and E3 ubiquitin ligases. Subsequently, RIPK1 undergoes polyubiquitination, which facilitates the formation of complex II, comprising FADD, caspase-8, RIPK1, RIPK3, and mixed lineage kinase domain-like protein (MLKL), all of which are crucial for mediating necroptosis. Notably, the inactivation of caspase-8 is essential, as it enables RIPK1 to acquire enzymatic activity and interact with RIPK3 to form complex II. Within this complex, RIPK3 phosphorylates MLKL, ultimately triggering necroptosis by compromising plasma membrane integrity. Additionally, necroptosis can be initiated in caspase-deficient cells through the activation of pattern-recognition receptors (PRRs), such as Toll-like receptors 3 and 4 (TLR3 and TLR4) and Z-DNA-binding protein 1 (ZBP1) [56]. The dysregulation of necroptosis has significant implications for various diseases, highlighting its potential as a therapeutic target in cancer.

In various cancers, RIPKs have emerged as key regulators of necroptosis, a programmed form of necrotic cell death with therapeutic relevance. Dysregulation of RIPK3 has been frequently observed in tumor cells, including those from colorectal, breast, and lung cancers, contributing to impaired necroptotic signaling and enhanced tumor survival [57–59]. Restoration of RIPK3 expression can reactivate the epigenetic modifications of MLKL and induce necroptosis, thereby suppressing tumor growth [60]. In some cancers, RIPK3 levels are elevated during early disease stages and inversely correlated with tumor burden and biomarkers of malignancy, suggesting a tumor-suppressive role in the initial phases of oncogenesis [61]. Natural compounds such as Erigeron breviscapus have been shown to induce necroptosis in cancer cells by activating the RIPK1–RIPK3–MLKL signaling axis, highlighting their potential as necroptosis-based therapeutic agents [62].

Furthermore, members of the sirtuin (SIRT) family, particularly SIRT3, have been implicated in modulating necroptotic responses in cancers. Biologically, SIRTs exert nicotinamide adenine dinucleotide $(NAD)^+$-dependent deacetylase activity on a range of substrates, including transcription factors, metabolic enzymes, and chromatin-associated proteins, thereby influencing cellular stress responses and cell death pathways. In the context of necroptosis, SIRT3-mediated deacetylation of mitochondrial proteins may enhance ROS production, which promotes RIPK1/RIPK3 activation [63]. Consequently, elevated SIRT levels can potentiate necrosome assembly and downstream MLKL phosphorylation. Elevated expression of these SIRTs has been associated with advanced tumor features, such as lymph node metastasis, higher histological grades, and reduced patient survival in several malignancies, including lung cancer, colorectal cancer, and PCa models [64–66]. These findings underscore the multifaceted role of necroptotic regulators like RIPKs and SIRTs in cancer biology and point toward their potential exploitation for therapeutic intervention across a broad oncologic spectrum.

Necroptosis and apoptosis, sharing some common characteristics, can be simultaneously modulated as "PANoptosis" in cancers. For instance, the loss of reticulocalbin 1 (RCN1) induces apoptosis in AR-negative DU145 cells but promotes necroptosis in AR-expressing LNCaP cells [67]. Nevertheless, the authors suggest that this dual effect does not occur through the regulation of AR expression or androgen levels. They reported that RCN1 simultaneously regulates apoptosis and necroptosis by modulating PTEN/Akt and CaMKII activity, respectively. It is indicated that caspase-8 activity should be further explored based on the fundamental mechanisms underlying the occurrence of apoptosis and necroptosis. Additionally, there is growing evidence that ZBP1-induced apoptosis may be accompanied by necroptosis, emphasizing the complex role of ZBP1 in regulating cell death in multiple cancer models [68, 69].

2.3 | Autophagy: Cellular Recycling and Survival Strategy

Autophagy is an evolutionarily conserved catabolic process that facilitates the degradation and recycling of intracellular components, playing a fundamental role in cellular homeostasis

and stress adaptation. Autophagy exists in three primary forms, chaperone-mediated autophagy, microautophagy, and macroautophagy, characterized by distinct mechanisms of cargo delivery to lysosomes [70]. The term "autophagy," derived from the Greek words autos (self) and phagein (to eat), captures the essence of this "self-eating" process, meaning delivering cytoplasmic cargo to the lysosome for degradation. This cellular process degrades and recycles cytoplasmic components, including organelles and protein aggregates, through the formation of autophagosomes that subsequently fuse with lysosomes. This recycling is essential for cellular energy maintenance, and dysregulation of autophagy is implicated in various diseases, such as cancer and neurodegeneration [71, 72]. Autophagy is classified into two distinct functional categories: autophagy-dependent cell death (ADCD) and autophagy-mediated cell death (AMCD). ADCD refers to scenarios in which cell death is directly driven by the autophagy machinery, often due to excessive or dysregulated autophagic activity that leads to critical loss of cellular components. Conversely, AMCD denotes cases in which autophagy modulates or intersects with other dominant cell death pathways, such as apoptosis, necrosis, or pyroptosis, without being the primary cause of death [73]. For example, studies found that autophagy-dependent ferroptosis via ferritinophagy and lipophagy is increasingly validated in cancer pathogenesis and treatment, which is a classical unique AMCD [74–76].

At the molecular level, autophagy is orchestrated through a series of highly regulated steps involving numerous signaling pathways and autophagy-related genes (ATGs). The AMP-activated protein kinase (AMPK)–mechanistic target of rapamycin complex 1 (mTORC1) axis plays a central role in initiating autophagy by promoting the formation of isolation membranes. The Beclin-1/VPS34 complex is then recruited to drive vesicle nucleation and expansion. c-Jun N-terminal kinase (JNK)-mediated phosphorylation of BCL-2 and BIM results in the dissociation of Beclin-1, further enhancing VPS34 activity. Subsequent vesicle elongation is mediated by the ATG12–ATG5–ATG16L complex and the lipidation of microtubule-associated protein 1A/1B-light chain 3 (LC3), a process converting LC3-I to the autophagosome-integrated form LC3-II. Upon completion, autophagosomes fuse with lysosomes to form autolysosomes, enabling cargo degradation and recycling. Multiple upstream signaling cascades also converge on autophagy regulation, including EGFR/Ras/MEK/ERK, JNK/c-JUN, p38/MAPK, and Wnt/β-catenin pathways, which integrate extracellular and intracellular cues to fine-tune autophagic flux [77]. Together, these coordinated molecular events position autophagy as a critical regulator of cell survival and death under both physiological and pathological conditions.

Recent foundational studies have illuminated the intricate interplay between autophagy and several key molecular pathways involved in cancer progression. Among these, SIRTs have emerged as critical regulators of diverse forms of PCD, including apoptosis, necroptosis, and autophagy. SIRTs modulate autophagic processes by targeting essential components such as Beclin1, LC3, and ATG proteins, while also influencing cellular energy metabolism and stress response pathways [78, 79]. In multiple cancer models, including pancreatic ductal adenocarcinoma (PDAC), lung cancer, and endometrial cancer (EC), SIRTs ablation has been shown to inhibit tumor cell proliferation and invasion via autophagy and disrupting cellular homeostasis [80–82]. Meanwhile, in genetically engineered mouse models, deletion of SIRT1 impaired autophagosome maturation and reduced autophagic flux, which led to the development of premalignant lesions, such as intraepithelial neoplasia and similar early-stage neoplasias in other tissues [83]. In addition, SIRT1 deficiency has been associated with diminished mitophagy via regulation of the PINK1/Parkin pathway in cancers, further contributing to aberrant cell survival and transformation [81, 84, 85]. These findings collectively suggest that SIRTs serve as molecular "gatekeepers" of autophagy, limiting early oncogenic events and supporting their role as potential therapeutic targets across a wide range of cancers.

Androgen receptor (AR) signaling is another critical regulator of cancer-related autophagy, especially in PCa. Recent studies have reported that small extracellular vesicles derived from prostate stromal cells enhance the radioresistance of PCa cells through the AMPK-activated autophagy pathway, with stromal cells secreting higher levels of IL-8 compared with AR-positive PCa cells, such as LNCaP [86]. Besides, AR-related autophagy has been observed across various clinical stages of the disease. The TOMM20-triggered autophagic degradation, which is positively correlated with AR expression, can facilitate the transformation to neuroendocrine PCa (NEPC) [87]. Additionally, the regulation of expression by YAP1 appears to be influenced by autophagy activity in castration-resistant PCa (CRPC), an advanced stage of PCa that continues to progress despite hormone therapy [88]. Thus, autophagic signaling exerts an imperative role both in the early stages of tumorigenesis and the progression of PCa. The role of autophagy in PCa is complex, as it can function as a survival mechanism or contribute to cell death, depending on the cellular context [89]. The interplay between autophagy and other PCD pathways, such as resistance to anoikis induced by cell detachment from the extracellular matrix, is mediated by the CEMIP signaling pathway through protective autophagy [90, 91]. Understanding and modulating the intricate mechanisms of autophagy in cancers presents a promising avenue for therapeutic exploration.

2.4 | Pyroptosis: Inflammatory Damage-Triggered Cell Death

Pyroptosis, categorized alongside apoptosis and necroptosis as a form of PANoptosis, is an inflammatory PCD [92]. PANoptosis is characterized by its inflammatory nature and involves signaling complexes including ZBP1, caspase-8, and RIPK1/3 [93, 94]. The interconnectedness within PANoptosis arises from the initiation of these processes through some common receptors (e.g., PRRs) and their reliance on the cleavage functions of caspases. In contrast, pyroptosis is specifically defined by its dependence on caspase-1 and the formation of gasdermin pores in the plasma membrane, which are essential for its inflammatory effects [95]. In the canonical inflammasome pathway, both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) stimulate intracellular signaling molecules, leading to the assembly of inflammasomes composed of procaspase-1. This complex activates caspase-1, which along with caspase-4/5, cleaves gasdermin D (GSDMD), resulting in pore formation and the release of proinflammatory cytokines such as interleukin-1 beta (IL-1β) and interleukin-18

(IL-18) that trigger subsequent cell lysis and execute pyroptosis. Besides, caspase-11 can induce pyroptosis independent of caspase-1 in a noncanonical pathway [96]. Dysregulation of pyroptosis has been implicated in various pathological conditions, including autoimmune diseases, inflammatory diseases, and cancers. Understanding the molecular mechanisms of pyroptosis is vital for developing targeted therapies.

The degree of pyroptotic activity varies markedly across cancer types and stages. A pan-cancer analysis identified differential expression of 17 pyroptosis-related genes, with higher expression levels associated with enhanced immune infiltration in "hot" tumors and poorer pyroptosis in "cold" tumors [97]. In gastric cancer, patients with low pyroptosis risk scores exhibited increased antitumor immune infiltration and better responses to neoadjuvant immunotherapy [98]. Similarly, in urological carcinomas, stratification based on pyroptosis gene signatures revealed subtypes with significant prognostic and immunologic differences [99, 100]. The pyroptosis cascade is modulated by several regulators, including caspases (especially caspase-1/4/5/11), gasdermins (GSDMD, gasdermin E [GSDME]), and upstream inflammasomes. Dysregulation often involves genetic or epigenetic silencing of key components. For instance, USP48 was shown to stabilize GSDME, promoting pyroptosis and enhancing immunotherapy efficacy, suggesting its potential as a therapeutic target [101]. Additionally, noncoding RNAs and epigenetic mechanisms (e.g., DNA methylation) were found to regulate pyroptosis-related gene expression, further influencing tumor progression and immune responsiveness [102].

Pyroptosis predominantly affects phagocytic cells like macrophages and has been implicated in cancer progression and treatment. The compound C10 was found to initiate pyroptosis in PCa by activating caspase-3 and the PKCδ/JNK pathway, leading to GSDME cleavage and concurrent apoptosis and pyroptosis in PCa cells [103]. Hypermethylation of the GSDME promoter and reduced GSDME expression in PCa tissues are linked to a diminished response to PARP inhibitors [104]. Furthermore, GSDME-mediated pyroptosis can be modulated by CDC20, which promotes GSDME ubiquitination [105]. Resistance to apoptosis may reduce pyroptosis sensitivity, and increased methionine levels are identified as antipyroptotic in "persister" cells, which exhibit a proliferative advantage under pyroptotic conditions [106]. Other anti-inflammatory factors, including canopy FGF signaling regulator 3 (CNPY3) and the NOD-like receptor family pyrin domain containing 3–caspase-1–ASC complexes, have been shown to induce pyroptosis as an antitumor mechanism in cancers [107, 108]. The growing evidence for the antitumor effects of pyroptosis positions the targeting of pyroptotic or combined PANoptotic cell death as a promising therapeutic approach for cancer.

2.5 | Entosis: Adhesion-Driven Cellular Cannibalism

Entosis is a nonapoptotic cell death phenomenon in which one cell engulfs another, leading to internalization and subsequent lysosomal degradation [109]. The molecular mechanisms underlying entosis are centered around cell-cell adhesion and actomyosin contractility, both of which are regulated by the RhoA–Rho-associated protein kinase (ROCK) signaling pathway. This pathway is activated in response to various triggers, including loss of matrix adhesion, expression of E-cadherin, and metabolic stress. The process begins with the formation of cell adhesions between the prospective host cell and the cell designated for internalization, primarily mediated by cadherin molecules. Following adhesion, actomyosin contractility driven by RhoA and ROCK, facilitates the internalization of the engulfed cell. The differential mechanical deformability between the two cells serves as the driving force for entosis [110]. Additional regulatory mechanisms involve AMPK, stress kinases such as JNK and p38, oncogenes such as KRas and c-Myc, and tumor protein p53 (TP53). In cancers, entosis has been observed and is believed to promote disease progression by enabling more aggressive cells to internalize and eliminate aggressive counterparts [111]. Understanding the molecular mechanisms of entosis is important for developing targeted therapies, as this form of cell death is implicated in cancer progression and may present distinct vulnerabilities that can be exploited therapeutically.

Entosis can be induced by multiple intrinsic and extrinsic stressors, including matrix detachment, glucose starvation, mitotic arrest, and chemotherapeutic drugs like paclitaxel [112, 113]. In breast, colorectal, and pancreatic cancers, entosis occurs more frequently under conditions that favor cellular stress and competitive interactions among tumor cells. For instance, pancreatic tumors show a higher prevalence of entotic CICs in liver metastases compared with primary tumors, suggesting that entosis may be selectively activated during cancer dissemination [114]. The initiation and progression of entosis depend on actin-myosin contraction in the internalizing cell, driven by Rho–ROCK signaling and modulated by cellular adhesion molecules like E-cadherins and P-cadherins [111]. Loss of RND3/RhoE in hepatocellular carcinoma enhances entosis through LAMP1 upregulation, implicating lysosomal activity in both initiation and degradation stages of the process [115]. Calcium signaling via Orai1 channels and cytoskeletal regulators like SEPTIN also contribute to the contractility and engulfment mechanics of entosis [116].

Entosis has paradoxical roles in tumor progression. On one hand, it promotes tumor suppression by killing genetically aberrant or detachment-prone cells. On the other hand, it fosters tumor evolution by promoting aneuploidy, enhancing nutrient scavenging, and enabling survival under stress [117]. In PDAC, entosis is linked to the formation of aggressive subclones marked by NET1 overexpression, which drives enhanced proliferation, metastasis, and resistance to anoikis [24]. Similar associations have been observed in breast and colorectal cancers, where high CIC frequency correlates with poor prognosis and metastatic potential [118, 119]. Wen et al. [120] found that the AR can enhance entosis in CRPC via the Rho/ROCK pathway. Although the role of AR in cell death regulation is recognized, the specific process of entosis in tumor cells is not fully understood. Entosis may serve as a survival mechanism in some tumor cells under pro-oxidant anticancer treatments [121]. In metastatic PCa, resistance to oxidative stress was accompanied by an increase in average cell size and polyploidization due to entosis, which facilitated the long-term survival of cancer cells [122]. Entosis also has implications for cancer treatment. Liu et al. [123] showed that the tyrosine kinase inhibitor (TKI) nintedanib promotes entosis via

the CDC42/ROCK pathway, and combining abiraterone with the Plk1 inhibitor onvansertib induced mitotic cancer cell death and entosis in abiraterone-resistant metastatic CRPC mouse models independently of AR signaling. The research informed a phase II clinical trial (NCT03414034) and highlights the potential for manipulating entotic cell death in cancer therapy [124].

2.6 | Ferroptosis: Fe-Dependent Cell Death via Overwhelming Peroxides

Ferroptosis, a form of PCD characterized by Fe-dependent lipid peroxidation, was first identified by Stockwell et al. [125]. Unlike apoptosis or necrosis, ferroptosis is characterized by the accumulation of lethal lipid peroxides, a process tightly regulated by the interplay between redox homeostasis, Fe metabolism, and membrane lipid composition. The initiation of ferroptosis hinges on an imbalance between proferroptotic processes and cellular antioxidant defenses. On the proferroptotic side, the biosynthesis and peroxidation of polyunsaturated fatty acid-containing phospholipids (PUFA-PLs) are key events, orchestrated by enzymes such as long-chain acyl-CoA synthetase 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3). Concurrently, Fe-dependent mitochondrial metabolism contributes to ROS generation and lipid peroxidation. In contrast, ferroptosis is counteracted by a suite of protective mechanisms, including the incorporation of monounsaturated fatty acids into phospholipids and both glutathione peroxidase 4 (GPX4)-dependent and independent antioxidant systems, which function to detoxify lipid hydroperoxides [126]. When the oxidative burden surpasses the capacity of these defense systems, lipid peroxides accumulate and initiate membrane damage in an Fe-catalyzed reaction, culminating in ferroptosis. Pharmacologically, this pathway can be manipulated using ferroptosis inducers (FINs). For example, erastin induces ferroptosis by inhibiting the cystine/glutamate antiporter system xc^-, thereby depleting intracellular glutathione (GSH). The clinically applied kinase inhibitor sorafenib also induces ferroptosis via suppression of solute carrier family 7 member 11 (SLC7A11), the most important component of system xc^- [127]. Growing evidence implicates ferroptosis in the pathogenesis of cancer, neurodegenerative disorders, and other diseases, and ferroptosis-related pathways are increasingly recognized as promising therapeutic targets in cancer, highlighting the potential for exploiting ferroptosis modulation in precision medicine approaches. Given the complicated disease conditions during PCa progression [128], the role of ferroptosis in PCa is provided to better comprehend this type of PCD (Figure 2).

Tumor cells with high Fe dependence, such as in TNBC and pancreatic cancer, exhibit heightened sensitivity to ferroptotic triggers [21]. Ferroptosis can be induced by pharmacological agents (e.g., erastin, RSL3), radiation, and cytokines like IFN-γ and TGF-β [129]. Transcription factors such as NF-E2-related factor-2 (Nrf2) promote resistance to ferroptosis by upregulating antioxidant responses, while tumor suppressors like p53 can either enhance or inhibit ferroptosis depending on cellular context [21]. Additionally, tumor microenvironmental factors, such as lactate, glutamate, and immune cells, also modulate ferroptosis sensitivity [130]. Ferroptosis suppressor protein 1 (FSP1), previously known as AIFM2, provides a GPX4-independent defense by regenerating reduced coenzyme Q10 (CoQ10), a lipophilic antioxidant, via NAD(P)H. FSP1 can prevent ferroptosis even in GPX4-deficient cells and contributes to resistance in certain tumor types [131]. Induction of ferroptosis can eliminate mesenchymal and drug-resistant cancer cells, offering a strategy against apoptosis-resistant tumors. Paradoxically, ferroptosis-induced inflammation may lead to immunosuppression in some contexts, thereby promoting tumor progression [21].

Hangauer et al. [132] revealed that patient-derived cancer organoids with mesenchymal traits linked to neuroendocrine transformation (NET) were sensitive to GPX4 inhibition. Meantime, Viswanathan's work highlighted that lipid peroxidase pathway inhibition is prevalent in therapy-resistant cancers, suggesting GPX4 and lipid peroxidation as therapeutic targets to combat drug resistance [133]. Subsequent studies identified regulators of GPX4 in PCa, such as serum/glucocorticoid regulated kinase 2 (SGK2), which can suppress ferroptosis and promote PCa metastasis by inhibiting FOXO1 effects on GPX4 [134]. More recent studies indicate that the GPX4-mediated antiferroptosis effect can be suppressed by tripartite motif 36 (TRIM36) [135], low-dose antimony treatment [136], or AR inhibition [137], which reverses the NET process and has demonstrated effectiveness in treating cancers. These studies have delineated the role of GPX4 as a crucial regulator of ferroptosis and a potential therapeutic target in cancers, with GPX4 inhibition showing promise, particularly in counteracting tumor growth, therapy resistance, and phenotype differentiation. In addition to GPX4, our latest study revealed that the activation of PLK1/TP53–SAT1 axis targeted by ezetimibe-engineered compound obviously induced ferroptosis and suppressed tumor growth and invasion in PCa [138]. Another contemporary study also reported the ferroptosis-mediated cancer suppression by the combinational treatment of ezetimibe and PARP inhibitor in TNBC [139].

In the lipid metabolism-associated processes of ferroptosis, it has been widely recognized that the accumulation of PUFAs in the membrane determines the cellular sensitivity to peroxidation and the outcome of ferroptosis. The peroxidation propensity PUFAs surpasses that of monounsaturated and saturated fatty acids. Enzymes such as ACSL4 and LPCAT3, implicated in various cancers, activate and integrate PUFAs into cellular membranes to drive ferroptosis [140]. Among the limited studies, enzalutamide treatment has been shown to increase PUFA content and ferroptosis susceptibility in PCa cells by enhancing lipid uptake [141]. High ACSL4 and LPCAT3 expression enhances ferroptosis susceptibility in TNBC, hepatocellular carcinoma, and renal cell carcinoma through lipid reprogramming [142–144]. Castillo et al. [145] reported that the ACSL4 inhibitor PRGL493 suppresses cell growth and sensitizes them to chemotherapy and hormone treatment. Thus, an expanding body of evidence has confirmed the role of ACSL4-induced ferroptosis in regulating tumor biology in a variety of circumstances. Further research is anticipated to explore this as a potential therapeutic direction.

2.7 | Cuproptosis: Accumulative Cu-Induced Cell Death

Cu, an essential micronutrient, is tightly regulated by proteins such as Cu transport protein 1 (CTR1) and six-transmembrane epithelial antigen of the prostate (STEAP), with dysregulation

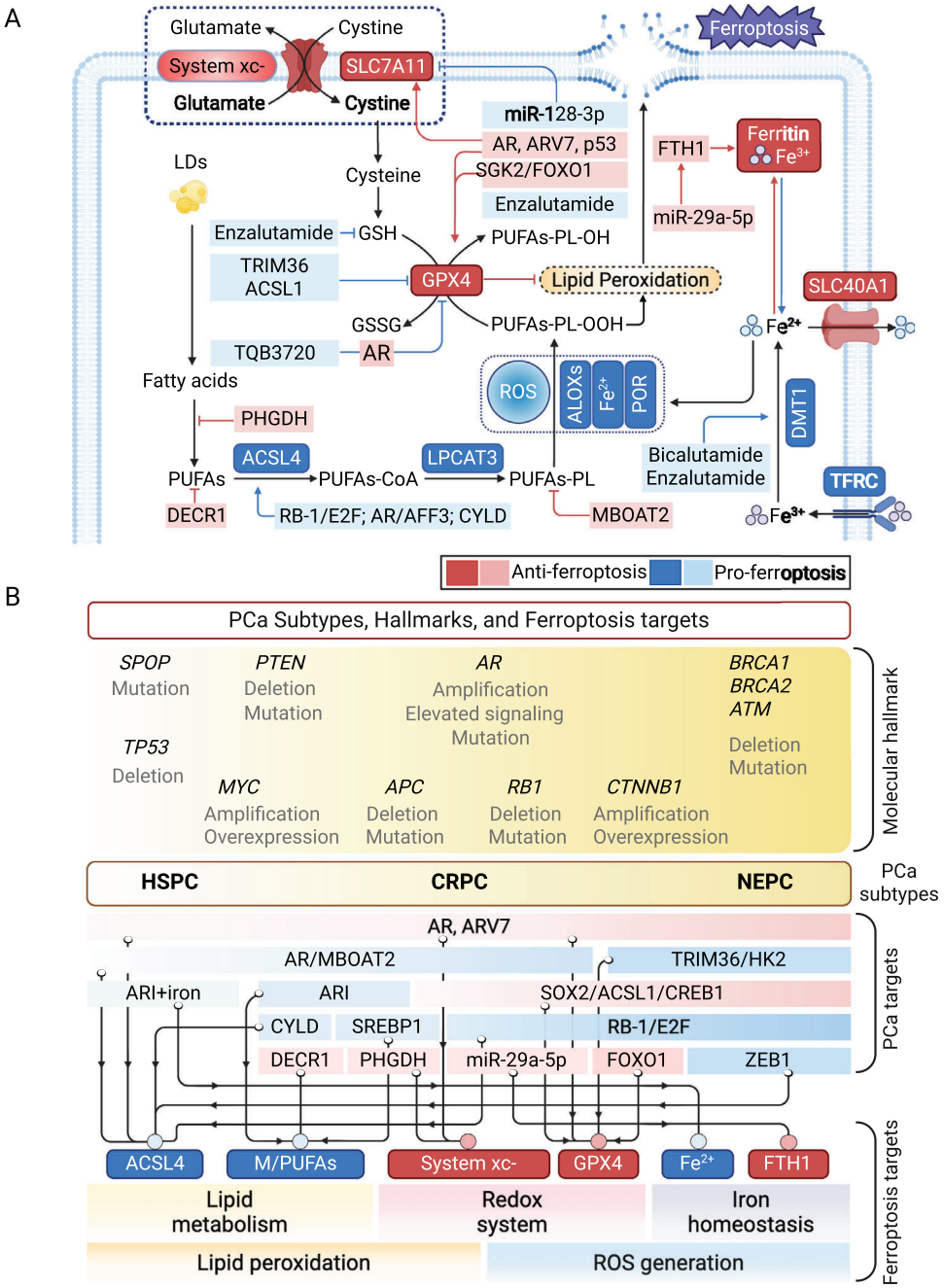


FIGURE 2 | Ferroptosis pathway and cancer subtype-related targets in PCa. (A) Canonical ferroptosis pathway and representative targets or drugs reported in PCa. The transporter system xc^- facilitates the entry of cystine into cells while simultaneously exporting glutamate. Inside the cells, cystine is converted to cysteine, which is utilized to produce GSH. GPX4 can convert lipid hydroperoxides into lipid alcohols, which makes the GSH–GPX4 system a crucial part in protecting cells against ferroptosis. A variety of proteins, including TFRC, SLC40A1, and components of ferritin (FTH1 and FTL), regulate ferroptosis by managing iron homeostasis. The synthesis of fatty acids, mediated by ACAC or the release of fatty acids through lipophagy, leads to an increase in intracellular free fatty acids, which in turn drives ferroptosis. ACSL4 and LPCAT3 enhance the integration of PUFAs into phospholipids, creating PUFAs-PL that are susceptible to oxidation triggered by free radicals and mediated by ALOXs. Red and blue blocks represent anti- and proferroptosis factors, respectively. (B) Hallmarks of PCa subtypes and related regulators in ferroptosis-targeted therapy. The hallmarks of PCa and targets in ferroptosis are shown in parallel with their corresponding clinical subtypes, including HSPC, CRPC, and NEPC. The regulatory targets are then assigned to the core processes of ferroptosis, including lipid peroxidation and ROS generation. Red and blue blocks represent anti- and proferroptosis factors, respectively. Targets specifically reported in PCa include AR, MBOAT2, TRIM36, SGK2/FOXO1, miR-29a-5p, and so on. *Abbreviations*: TFRC: transferrin receptor; SLC40A1: solute carrier family 40 member 1; ACAC: acetyl-CoA carboxylase; FTL: ferritin light chain; PUFAs-PL: PUFA-enriched phospholipids; ALOXs: 5-lipoxygenases. HSPC: hormone-sensitive prostate cancer; CRPC: castration-resistant prostate cancer; NEPC: neuroendocrine prostate cancer. The plot was created by BioRender.

implicated in diseases like Wilson's disease and cancer [146, 147]. In 2022, Tsvetkov et al. [3] identified a novel form of PCD triggered by intracellular Cu overload, which they termed cuproptosis. Unlike previously characterized PCD forms, cuproptosis operates through a unique mechanism and is resistant to inhibitors of apoptosis, necroptosis, ferroptosis, and other classical pathways. Only Cu chelators were effective in suppressing this Cu-induced cytotoxicity, highlighting its mechanistic distinction [3]. Mechanistically, cuproptosis is initiated by the interaction of Cu ions with lipoylated components of the tricarboxylic acid (TCA) cycle, leading to protein aggregation and cellular stress. The Cu ionophore elesclomol (ES) facilitates the transport of Cu(II) to the mitochondria, where ferredoxin 1 (FDX1) reduces it to Cu(I). Accumulated Cu(I) interacts with lipoylated dihydrolipoamide S-acetyltransferase (DLAT), inducing protein oligomerization and aggregation. Simultaneously, Cu accumulation destabilizes Fe–sulfur (Fe–S) cluster-containing proteins, contributing to mitochondrial dysfunction and oxidative stress [148]. The defining hallmark of cuproptosis is the Cu-dependent aggregation of lipoylated mitochondrial enzymes alongside the loss of Fe–S cluster proteins. This dual disruption ultimately leads to metabolic collapse and cell death. Aberrant Cu accumulation and its downstream effects have been linked to a range of pathological conditions, including tumorigenesis, suggesting cuproptosis as a potential target for therapeutic intervention in cancer and other diseases [149].

Cu's role in cancer cell death has a history dating to the 1980s, with disulfiram and ES as key Cu ionophores that induce melanoma cell death [150, 151]. Studies have implicated mitochondrial dysfunction and ROS in this process. However, applying the ROS inhibitor N-acetylcysteine showed that ROS may not be the sole cause of Cu cytotoxicity [152]. Wen et al. [153] demonstrated that inducing cuproptosis can enhance the chemotherapeutic response of prostate tumors to docetaxel by inhibiting autophagy via the DLAT/mTOR pathway, which showed the connectivity between cuproptosis and other forms of cell death. Cuproptosis susceptibility is tightly linked to mitochondrial metabolism and Cu homeostasis. Tumors with high oxidative phosphorylation activity, such as clear-cell renal cell carcinoma and PCa, exhibit greater sensitivity to cuproptosis-inducing agents [154, 155]. In contrast, cancer stem cells (CSCs) in TNBC resist cuproptosis due to hypoxia-mediated downregulation of FDX1, although this can be overcome by nanomaterial-assisted photothermal therapy [156]. Cuproptosis also reshapes the tumor immune microenvironment. In colorectal and bladder cancers, cuproptosis-associated gene signatures correlate with distinct immune infiltration patterns and predict response to immune checkpoint blockade [157, 158]. Furthermore, cuproptosis can enhance $CD8^+$ T cell cytotoxicity by reducing PD-L1 expression and suppressing Wnt/β-catenin signaling in microsatellite-stable colon cancer, overcoming immune resistance [159, 160].

Cuproptosis-based therapies hold promise, especially in tumors resistant to apoptosis or ferroptosis. Predictive cuproptosis gene signatures have been developed for gastric, ovarian, and BCas to guide prognosis and drug response prediction [161–163]. Cu-based nanomaterials have emerged as potent delivery systems to enhance tumor-specific cuproptosis while minimizing systemic toxicity [164]. The AR antagonists also showed efficacy in inducing cuproptosis in treating cancers. Gao et al. [165] found that enzalutamide treatment enhanced the susceptibility of CRPC cells to cuproptosis by increasing their mitochondrial dependency. This vulnerability is specifically reversed using the Cu chelator tetrathiomolybdate, which binds to Cu ions and mitigates the cellular stress induced by Cu overload [165]. Despite these findings, the limited foundational research on cuproptosis in cancers constrains our understanding of its regulatory mechanisms and therapeutic potential, underscoring the need for further in-depth studies.

2.8 | Disulfidptosis: Unique Cell Death by Glucose Starvation in Cancer Cells

Disulfidptosis is a recently characterized form of PCD that occurs under conditions of glucose deprivation or impaired glucose uptake, specifically in cells with elevated expression of the cystine/glutamate antiporter subunit SLC7A11. This unique vulnerability was investigated by Liu et al. [5], who sought to clarify the mechanisms underlying rapid cell death in $SLC7A11^{high}$ cancer cells. Under glucose-starved conditions, $SLC7A11^{high}$ cells experience excessive cystine uptake, which is intracellularly reduced to cysteine, a reaction that consumes large amounts of NADPH. The resultant NADPH depletion impairs the cell's redox balance, leading to the accumulation of disulfides and the induction of disulfide stress. Such stress activates the Rac–WRC–Arp2/3 signaling pathway, contributing to the formation of aberrant disulfide bonds in actin cytoskeleton proteins. This results in the collapse of F-actin and detachment from the plasma membrane, ultimately culminating in cell death. The process is distinct from well-known forms of cell death, such as apoptosis, necroptosis, and ferroptosis [5]. Its selective dependence on metabolic and redox imbalances in $SLC7A11^{high}$ cancer cells underscores its potential as a therapeutic target, particularly in tumors with dysregulated cystine metabolism and high oxidative stress.

SLC7A11, also known as xCT, is a crucial member of the cystine transporter solute carrier family. Overexpression of SLC7A11 is commonly observed in cancer cells, where it facilitates cystine uptake, thereby protecting these cells from oxidative stress and ROS-mediated cell death, including ferroptosis. Consequently, SLC7A11 has been regarded as a significant regulator that facilitates tumor survival and progression [166]. Nevertheless, a contemporaneous study found that varying levels of SLC7A11 overexpression led to distinctly different outcomes for cancer cells. Alongside research on disulfidptosis, these findings further elucidate the complex roles of SLC7A11 overexpression in cancer [167]. According to Liu et al., the premise of manipulating overexpressed SLC7A11 as a driver of disulfidptosis is glucose starvation, which occurs in conditions of the hypoxic TME, or as a result of targeted therapies that inhibit glucose uptake or utilization, such as glucose transporter (GLUT) inhibitors [5]. Glucose starvation is an emerging hallmark of cell survival-related metabolic switches in cancer and may serve as a promising indicator of cellular sensitivity to various forms of cell death [169, 170]. Furthermore, ER stress has been identified as both a consequence and modulator of disulfidptosis, where its inhibition enhances cell death under glucose limitation [171]. Multiomics analyses reveal that disulfidptosis regulators are widely dysregulated across cancers due to DNA methylation changes and copy number variations,

TABLE 1 | Established markers, therapeutic targets, and biological hallmarks of various PCDs.

PCD type	Markers and targets	Biological hallmark
Apoptosis	BCLs, p53, Fas, TNFR1, DR4/5, IAPs, APAF1, caspase-3/7/8/9	Cellular stress and death receptor initiation mediated activation of effector caspases
Necroptosis	Nec-1, Fas, TNFR1, DR4/5, TLR, RIPK1/3, MLKL, ZBP1	Extracellular signal mediated complex formation consisted of RIPKs and MLKL
Autophagy	ATGs, AMPK, mTOR, LC3, Beclin-1, BCL-2, BIM	Maturation of the autophagosome and fusion with a lysosome to form an autolysosome
Pyroptosis	GSDMD, caspase-1/4/5/8, IL-1β, IL-18	Caspase-induced GSDMD cleavage, subsequent pore formation and proinflammatory cytokines secretion
Entosis	RhoA, ROCK, AMPK, JNK, p38, DR4/5	Cell engulfment triggered by detachment and contractile activity
Ferroptosis	GPX4, SLC7A11/xCT, ACSL4, LPCAT3, TFR1, PUFAs	Imbalance of redox system induces accumulation of lipid peroxides
Cuproptosis	FDX1, DLAT, Fe–S, CTR1, STEAP	Aggregation of lipoylated mitochondrial enzymes and decrease of Fe–S protein
Disulfidptosis	SLC7A11/xCT, GLUT, Rac–WRC–Arp2/3, SLC3A2	NADPH depletion and disulfides accumulation under glucose starvation and SLC7A11 overexpression

Abbreviations: IAPs, inhibitor of apoptosis proteins; APAF1, apoptotic protease-activating factor 1; Rac, Ras-related C3 botulinum toxin substrate; WRC, WAVE regulatory complex; Arp2/3, actin-related protein 2/3 complex; SLC3A2, solute carrier family 3 member 2.

influencing tumor progression and therapeutic responsiveness [172].

Strategies to induce disulfidptosis, such as combining GLUT inhibitors with ER stress modulators, have shown antitumor effects in vitro and in vivo [171]. Glycogen synthase 1 (GYS1) has also emerged as a therapeutic target to trigger disulfidptosis in TNBC [173]. To evaluate the potential of disulfidptosis in cancer therapy, Zhao et al. [174] integrated multiomics and pan-cancer approaches to construct a molecular landmark of tumor disulfidptosis across over 30 cancer types. Their experimental validation proved that disulfidptosis-related genes could be effectively targeted by various antitumor agents [174]. The crosstalk between disulfidptosis and ferroptosis, particularly involving the SLC7A11 and cystine system, has also been further elucidated in cancers [175, 176]. Disulfidptosis activity influences the tumor immune microenvironment (TME), with certain disulfidptosis subtypes showing enhanced $CD8^+$ T cell infiltration and improved immunotherapy response, notably in renal and cervical cancers [177, 178]. With more in-depth research into the mechanisms of disulfidptosis, novel insights could be gained to utilize disulfidptosis as a therapeutic target in addressing various challenges associated with PCa.

3 | Connectivity Between PCD

Cell death pathways are essential for maintaining cellular homeostasis and defending against diseases. Despite their distinct morphological and molecular characteristics, these pathways share commonalities and exhibit differences in their mechanisms, roles, and regulation (Table 1). We also summarize the molecular connections between major PCDs to illustrate their intrinsic crosstalk, as shown in Figure 3.

Initiation through membrane receptor activation is a common mechanism in many PCDs. Extrinsic apoptosis and necroptosis are both initiated by the activation of cell surface death receptors, such as TNFR1 and Fas, which trigger intracellular signaling cascades involving adaptor proteins and kinases. Besides, pyroptosis also shares PRRs-driven activation of signaling transduction with alternative necroptosis that responds to PAMPs and DAMPs [179]. It should be noted that caspase families, a group of cysteine proteases capable of cleaving substrates after aspartic acid residues, are extensively involved in multiple PCD forms such as apoptosis, necroptosis, and pyroptosis [180]. Notably, the differential activation of caspases distinguishes the fate of cell death in various contexts. Caspase-1 is a crucial initiator of pyroptosis; however, it does not participate in apoptosis. In contrast, the downstream caspases involved in apoptosis, such as caspase-3 and caspase-7, inhibit pyroptosis by inactivating GSDMD. Similarly, caspase-8 plays an essential role in facilitating both apoptosis and pyroptosis, while also serving as a critical inhibitor of necroptosis [6]. Furthermore, the interaction between BCL-2 and beclin-1, two key regulators in PCD, establishes a crucial molecular link between apoptosis and autophagy. Abundant studies have demonstrated that BCL-2 directly binds to beclin-1, and the abundance of this interaction significantly influences the level of cellular autophagic activity. Disrupting the BCL-2/beclin-1 binding has emerged as an effective strategy to enhance autophagy [181, 182]. Further mechanistic investigations suggest that beclin-1 itself may function as a BH3-only protein, inherently susceptible to inhibition by BCL-2, thereby underscoring its dual regulatory potential in PCD [183].

Another hallmark of PCD connection is the redox system imbalance and metabolism dysregulation, which are common causes of ion-mediated cell death, including ferroptosis, cuproptosis, and disulfidptosis. Ferroptosis and cuproptosis are classic metal

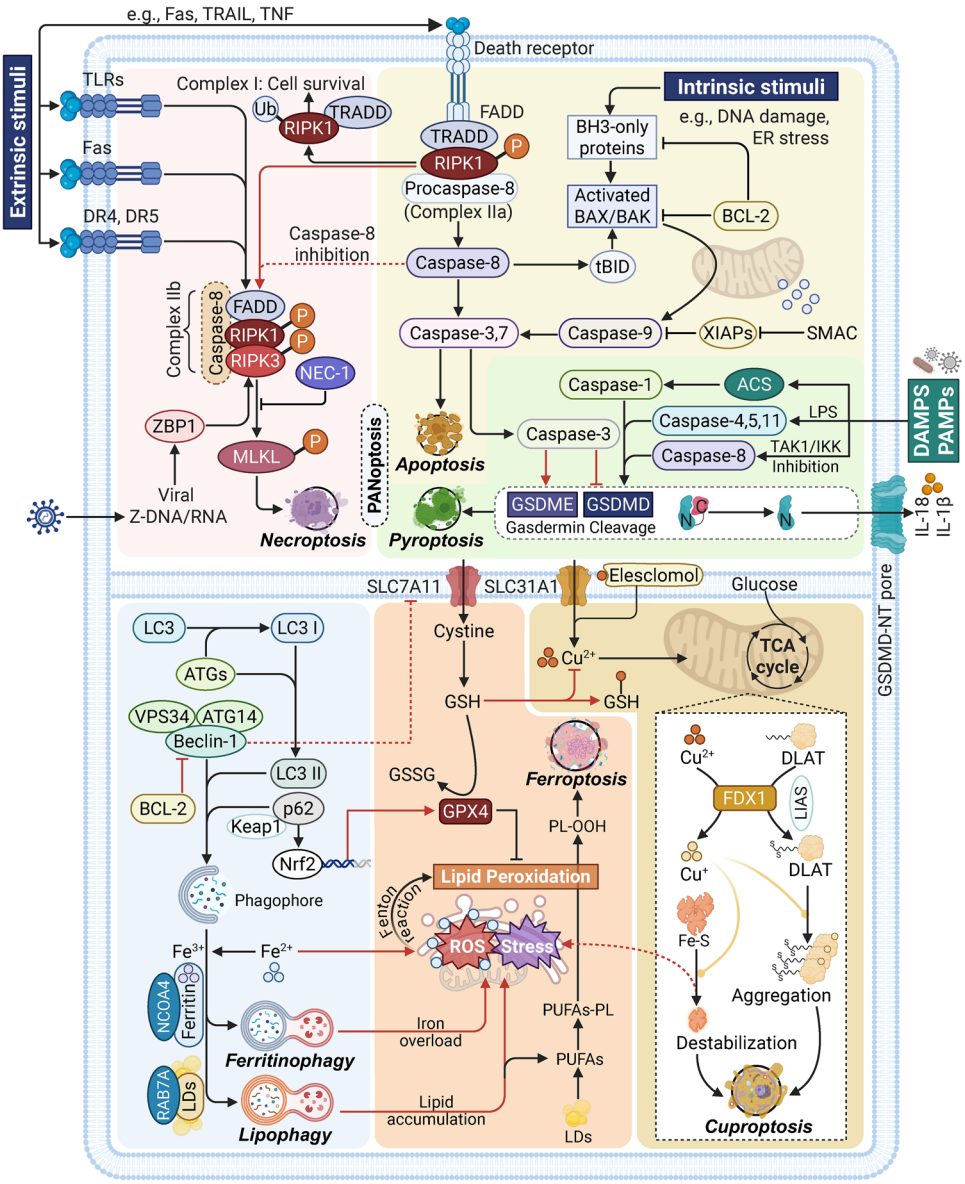


FIGURE 3 | Crosstalk between different PCD forms and their core mechanisms. This network illustration introduces 6 major forms of PCD indicated in the review, including apoptosis, necroptosis, pyroptosis, autophagy, ferroptosis, and cuproptosis. Apoptosis, necroptosis, and pyroptosis are closely linked and constitute the PANoptosis based on sharing molecular drivers such as RIPK1 and caspases family. The formation of different RIPK1–TRADD complexes (I, IIa, IIb) determines the PCD type and cell fate, including survival, apoptosis, and necroptosis. Caspase-8 is the common protein that participates in these three PCDs, making up PANoptosomes along with ZBP1 and ACS in PANoptosis. In autophagy, the driving factor beclin-1 has been recognized as a novel BH3-only protein that can be intrinsically suppressed by BCL-2, making up its association with apoptosis [183]. Next, autophagy tightly interacts with ferroptosis, especially in the form of ferritinophagy and lipophagy, which provide fundamental substrate iron and lipids to reinforce the core process (Fenton reaction and lipid peroxidation) of ferroptosis. The p62–Nrf2 pathway is another reverse regulatory approach on ferroptosis due to its transcriptional role on GPX4, as reported by the latest studies [139, 369, 370]. The GSH metabolism, involved in the ferroptosis redox system, can inhibit cuproptosis initiation by chelating copper(II). Finally, the destabilization of the Fe–S complex enhances the ROS level, strengthening the core process of autophagic, ferroptotic, and cuproptotic cell death. Blocks of different colors represent different PCDs. The red lines indicate the association between different PCDs. Abbreviations: ACS: apoptosis-associated speck-like protein, SMAC: second mitochondria-derived activator of caspases, XIAP: X-linked inhibitor of apoptosis protein, Ub: ubiquitination, P: phosphorylation, PL-OOH: phospholipid hydroperoxides, LDs: lipid droplets, NCOA4: nuclear receptor coactivator 4, RAB7A: RAS-related in Brain 7A. The plot was created by BioRender.

ion-dependent forms of PCD in which excessive levels of divalent Fe and Cu lead to lipid peroxidation and the aggregation of lipoylated proteins, respectively, resulting in cell death associated with toxicant overload. Disulfidptosis, driven by disorders in glucose metabolism and NADPH depletion, culminates in cell death related to the accumulation of disulfide bonds. The intrinsic connection between these forms of PCD, characterized by redox system imbalance and cellular metabolic disruption, can yield synergistic therapeutic effects in cancer treatment. For instance, two clinically utilized FINs, sorafenib and erastin, can significantly mediate cuproptosis by increasing the expression of FDX1 and reducing GSH synthesis in liver cancer [184]. Similarly,

PPARγ antagonists can activate both ferroptosis and disulfidptosis by upregulating heme oxygenase 1 (HMOX1) and SLC7A11 [185]. Increasing evidence shows that SLC7A11/xCT, one of the vital regulators of intracellular antioxidants, has become a focal point for the synchronous regulation of these metabolic disorder-associated PCDs [186]. Moreover, cellular stress responses and ROS-associated events are extensively implicated in various PCD-related biological processes, including apoptotic and autophagic mitochondrial dysfunction, ferroptotic lipid hydroperoxides, and cuproptotic TCA cycle disorders [187, 188]. Finally, there is substantial evidence of crosstalk in molecular signaling between cell death pathways, where they can be simultaneously modulated by certain upstream regulators, such as RCN1, the SIRT family, mTOR, PI3K/Akt, and MAPK signaling, as mentioned above [9, 189]. Understanding these commonalities and differences is crucial for the development of targeted therapies and for deciphering the complex interplay between cell death pathways in disease pathogenesis.

4 | Targeting PCD in Cancer Treatment

Understanding PCD mechanisms across diverse malignancies is critical for developing precise and effective cancer therapies. Contemporary oncologic management integrates surgery, RT, cytotoxic chemotherapy, immunotherapy, and hormone therapies that leverage distinct PCD pathways to counter tumor progression and resistance. Adjuvant RT and chemotherapy remain standard in intermediate- and high-risk tumors, inducing cell death primarily via DNA damage-triggered apoptosis and mitotic catastrophe [190]. In the past decade, immunotherapies, particularly ICIs (e.g., anti-PD-1/PD-L1, CTLA-4), have reactivated T cell-mediated cytotoxicity by enhancing extrinsic apoptotic signaling across melanoma, lung, and renal cancers [191]. In parallel, targeted therapies directed at oncogenic drivers (e.g., EGFR, ALK, BRAF, PARP) demonstrate that inhibiting kinase signaling or DNA repair can induce both apoptotic and nonapoptotic PCD forms, often synergizing with conventional agents [192].

The emergence of novel PCD modalities, such as ferroptosis, pyroptosis, and cuproptosis, has broadened the therapeutic landscape. Ferroptosis is being investigated using GPX4 inhibitors and agents that disrupt GSH homeostasis, particularly in therapy-resistant tumors [193]. Combination approaches based on metal ions have shown synergistic antitumor efficacy in preclinical models [194]. Collectively, these findings underscore the translational potential of modulating diverse PCD networks to overcome therapeutic resistance and advance next-generation cancer treatments (Table 2).

4.1 | Targeting Cell Death in Chemotherapy

Chemotherapy remains a foundational approach to cancer treatment, with increasing emphasis on its ability to engage PCD pathways to overcome resistance and improve outcomes. Traditional chemotherapeutic agents often act by inducing apoptosis, but novel strategies now exploit alternative cell death mechanisms such as necroptosis, ferroptosis, and autophagy to circumvent apoptosis resistance, a common trait in various tumors. Apoptosis is the most widely studied mechanism of chemotherapy-induced PCD. Many cytotoxic drugs trigger apoptosis through intrinsic or extrinsic pathways, and resistance to chemotherapy often stems from dysregulation of key apoptotic regulators like BCL-2, p53, and caspases [311]. Small molecules such as navitoclax and obatoclax that target antiapoptotic Bcl-2 family proteins are under investigation for enhancing chemosensitivity [312]. Necroptosis may offer advantages in apoptosis-resistant tumors such as glioblastoma and pancreatic cancer. Agents like shikonin have been explored for their necroptosis-inducing properties to enhance chemotherapy efficacy in vitro [313]. Chemotherapeutics such as doxorubicin and paclitaxel can modulate autophagy-related pathways to augment cytotoxicity in resistant BCa [314]. Besides, traditional Chinese medicine (TCM) has emerged as a therapeutic contender, with our study showing Qingdai decoction inhibits CRPC cell growth by dampening the AKT pathway, which is crucial for the occurrence of autophagy and apoptosis [315]. These results indicate that supplementary agents may help overcome chemotherapeutic resistance in refractory cancer patients.

Beyond apoptosis-centered PCD forms, ion-dependent cell death modalities such as ferroptosis and cuproptosis have garnered interest for their role in sensitizing resistant cancer cells. Chemotherapy agents such as cisplatin and doxorubicin have been shown to promote ferroptosis by depleting GSH and inhibiting GPX4, especially in breast, colorectal, and hepatocellular carcinomas [194, 316]. While still in early investigation stages, cuproptosis inducers have demonstrated the capacity to overcome resistance in preclinical models of various solid tumors when combined with standard chemotherapy [317]. Importantly, ferroptosis and cuproptosis exhibit significant molecular crosstalk. Recent evidence suggests that mitochondrial Cu overload can sensitize cells to ferroptosis via enhanced ROS production and GPX4 inhibition [318]. Combinatorial regimens of cuproptosis and ferroptosis inducers are now being tested with promising potential to overcome resistance mechanisms in TNBC and lung adenocarcinoma [319, 320].

Moreover, chemotherapy may indirectly contribute to immune evasion by inducing PD-L1 overexpression in the TME through NF-κB activation, as shown in ovarian and gastric cancers. This highlights the need for combining chemotherapy with ICIs to sustain antitumor immunity [321, 322]. Finally, nanomedicine represents a transformative direction in cancer chemotherapy by enabling the targeted delivery of agents that induce specific PCD mechanisms, reducing systemic toxicity while enhancing tumor specificity [317].

4.2 | Targeting Cell Death in Immunotherapy

Immunotherapy has revolutionized oncology by harnessing the body's immune system to recognize and eradicate tumor cells. Among these strategies, ICIs, particularly PD-1/PD-L1 axis blockade, have demonstrated long-lasting clinical efficacy across multiple cancers. Recent advances underscore that their therapeutic benefit is not only derived from immune activation, but also through the modulation and induction of diverse forms of PCD. Traditionally, the success of PD-1/PD-L1 blockade has been attributed to the reactivation of cytotoxic $CD8^+$ T cells,

TABLE 2 | Reported targets and mechanisms of the PCD-based treatment in cancers.

PCD type	Treatment	Target/Mechanism	Cancer type	Refs
Apoptosis	Castration + ADT	Antiandrogen, TGF-β activation	Prostate cancer	[195]
	CD24–CAR NK	BCL-2 signaling blockade	Testis, prostate, renal, bladder cancer	[196]
	Quercetin	Dual inhibition of Wnt3a/β-catenin and Akt/NF-κB pathway; modulation of MAPK/ERK and JAK/STAT3 pathways, etc.	Breast, colorectal, liver cancer, glioblastoma, osteosarcoma	[197–200]
	NKG2D–CAR T/NK + IL-7/IL-21	Activation of T cells and NK cells	Lung, prostate cancer, and glioblastoma	[201–203]
	Ultrasound + docetaxel	Increased cytotoxicity by ultrasound exposure	Liver, lung, prostate cancer	[204–206]
	Delta-tocotrienol (δ-TT)	ER stress and ROS production through JNK/p38 activation; p16/CDK4/cyclin D1 pathway activation, etc.	Bladder, nasopharyngeal, ovarian, pancreatic, prostate cancer	[207–211]
	Selenium	ROS/p53/Bax-mediated TRAIL activation; STAT3/JNK pathway activation	Colorectal, lung, ovarian, prostate cancer	[212–215]
	Ophiopogonin D′	RIPK1 and Bim activation; disrupting RGS4 overexpression; p53 activation	Thyroid, colon, prostate cancer	[216–218]
	Curcumin	p38 MAPK activation; IRON-chelating via TfR1/IRP1 activation; ROS induction, etc.	Breast, colorectal, liver lung, prostate cancer	[219–222]
	Celastrol	ROS induction; NF-κB/Akt inhibition and JNK activation; PRDX inhibition, etc.	Gastric, esophageal, liver, colorectal, prostate cancer	[223–227]
	Corosolic acid	IRE-1/JNK activation; JAK2/STAT3 activation	Breast, pancreatic, prostate cancer	[228–230]
Necroptosis	Shikonin	RIP3/p62/Keap1 complex; T cells infiltration; RIP1/RIP3 activation, etc.	Breast, bladder, bile duct, prostate cancer	[231–234]
	SMAC mimetics	TNF-α/TNFR1 signalling; MLKL expression	Bladder cancer, lymphoma	[235, 236]
	δ-TT	MLKL expression and translocation	Prostate cancer	[237]
	Ophiopogonin D’	RIPK1/MLKL signaling blockade	Prostate cancer	[216]
	Selenium	ROS induced-RIP1 regulation	Prostate cancer	[238]
	Photodynamic therapy	Increased oxidative stress	Liver, ovarian, prostate cancer	[239–242]
Autophagy	δ-TT	ER stress through pJNK/p38 activation; release of mitochondrial ROS	Liver, prostate cancer	[207, 243]
	Chloroquine/hydroxychloroquine	Autophagosome–lysosome fusions break and discontinue	Breast, colorectal, liver cancer	[244, 245]
	Curcumin	Iron deprivation; mitochondrial membrane rupture	Colorectal, lung, prostate cancer	[219, 246, 247]
	Celastrol	ER stress; ROS-mediated mitochondrial dysfunction	Breast, colorectal, prostate cancer	[248–252]
	High-dose DHT	AR/miR-493-3p/PARK2 pathway activation	Prostate cancer	[253, 254]
	Photodynamic therapy	Increased oxidative stress; ROS/JNK pathway activation	Breast, colorectal, prostate cancer	[255, 256]

(Continues)

TABLE 2 | (Continued)

PCD type	Treatment	Target/Mechanism	Cancer type	Refs
Ferroptosis	Erastin/RSL3	GPX4/SLC7A11 inhibition	Breast, bladder, gastric, kidney, prostate cancer	[257–261]
	Sorafenib	SLC7A11 inhibition; oxidative stress	Liver, cervical, kidney cancer	[262–265]
	Iron supplementation	Enhanced oxidative stress and lipid peroxidation	Breast, prostate cancer, melanoma, glioblastoma	[266–268]
	Statins	Mevalonate pathway downregulation and GPX4 inhibition; antitumor immunity activation; autophagy dependence, etc.	Breast, gastric, lung cancer	[269–272]
	Curcumin	GPX4 and SLC7A11 inhibition; HCAR1/MCT1/SREBP1 pathway, etc.	Breast, liver, lung, ovarian cancer	[247, 273–275]
	Ezetimibe	NPC1L1 inhibition; PLK1/TP53/SAT1 activation	Breast, prostate cancer	[138, 139]
	Flubendazole	P53-mediated SLC7A11 inhibition; downregulation of xCT and GPX4	Breast, prostate cancer, glioblastoma	[276–278]
	CAR-NK cells and nanoplatform	HER2 and PSMA targeting; GPX4/SLC7A11 inhibition	Breast, prostate cancer	[279–281]
	Nanoparticles (NP)	Excessive iron oxide supplementation; PUFAs peroxidation; GPX4 inhibition	Colorectal, prostate cancer, lymphoma, acute myeloid leukemia	[282–285]
	Polyphyllin I	Nrf2/FTH1 suppression; xCT/GPX4 inhibition; ERK/DNMT1/ACSL4 pathway activation	Gastric, liver, prostate cancer	[286–288]
	Sanguinarine	GPX4 inhibition; ROS/BACH1/HMOX1 pathway activation	Cervical, lung, prostate cancer	[289–291]
Cuproptosis	ES–Cu	Excessive copper accumulation; DLAT/mTOR pathway activation	Breast, colorectal, liver, prostate cancer	[153, 184, 292, 293]
	Copper complex NPs	Excessive copper-induced cytotoxicity; immune responses	Breast, colorectal, live, pancreatic, prostate cancer	[294–300]
Pyroptosis	Gambogic acid	ROS/P53/mitochondria/caspase-3 activation; SIRT1-mediated CNPY3 localization, etc.	Breast, colorectal, ovarian, prostate cancer	[108, 301–303]
	Chemotherapy	Caspase-1 and caspase-3 signaling activation	Breast, colorectal, esophageal, lung cancer	[104, 304–307]
	Methionine	GSDME degradation; preservation of plasma membrane integrity	Esophageal, liver, lung, prostate cancer, head and neck squamous cell carcinoma	[106, 308]
Entosis	Ultraviolet radiation (UV)	JNK and p38 stress-activated kinase signaling	Breast cancer	[309]
	Nintedanib	CDC42/ROCK signaling activation	Prostate cancer	[123]
	Onvansertib	Plk1 inhibition	Prostate cancer	[124]
Disulfidptosis	Natural products	SLC7A11/NADPH signaling targeting	Breast, liver cancer	[310]
	NU1025	DCS3 subtype sensitivity	Clear cell renal cell carcinoma	[310]

Abbreviations: CDK4, cyclin-dependent kinase 4; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PRDX, peroxiredoxin; IRE-1, inositol-requiring enzyme 1; Keap1, Kelch-like ECH-associated protein 1; SREBP1, sterol regulatory element-binding protein 1; PSMA, prostate-specific membrane antigen; DCS3, differential screening-selected gene aberrative in neuroblastoma 3.

leading to apoptosis of tumor cells. However, recent insights suggest that immune checkpoint inhibition also promotes non-apoptotic cell death forms [14]. Immune activation may also trigger pyroptosis and necroptosis, which release proinflammatory mediators like IL-1β and DAMPs. In parallel, pyroptosis facilitates an antitumor immune microenvironment and boosts the efficacy of immunotherapy. Inhibition of CDC20 potentiates antitumor immunity by triggering GSDME-mediated pyroptosis in tumor [105]. These processes amplify immune cell recruitment and potentiate ICI efficacy. Combinatorial induction of these death forms, termed PANoptosis, has been proposed to overcome immunotherapy resistance [323].

Chimeric antigen receptor (CAR)-based therapies, including CAR-T and CAR-NK cells, are being optimized to overcome immunosuppressive barriers in solid tumors. CAR-T therapies have shown efficacy in hematologic malignancies, but challenges such as cytokine release syndrome, T cell exhaustion, and immunosuppressive TME limit their effectiveness in solid cancers [324]. Innovations such as IL-7-expressing CAR-T cells have demonstrated improved persistence and reduced apoptosis of $CD8^+$ T cells by modulating BCL-2 signaling pathways, enhancing their cytotoxic durability [14]. CAR-NK platforms represent a promising next-generation approach, combining innate immunity with engineered antigen specificity. Compared with CAR-T cells, CAR-NK therapies offer advantages such as lower toxicity, lack of GvHD, and the ability to function independently of MHC presentation [325, 326]. CAR-NK cells targeting tumor-specific proteins such as CD24 and prostate-specific membrane antigen (PSMA) have shown robust induction of apoptosis in tumor cells via Fas–FasL signaling and perforin/granzyme B pathways [327].

Ferroptosis is tightly linked to immune modulation. $CD8^+$ T cells, activated by PD-1/PD-L1 blockade, enhance ferroptosis via IFN-γ-mediated suppression of SLC7A11 and GPX4, leading to oxidative damage in tumor cells [328, 329]. Moreover, ferroptosis itself stimulates immunogenic cell death (ICD), releasing DAMPs (e.g., HMGB1, ATP) that promote dendritic cell maturation and T-cell priming. Preclinical studies show that nanoplatforms combining ferroptosis inducers with anti-PD-L1 antibodies synergize to enhance antitumor responses [330–332]. Clinical relevance is further supported by findings that genes regulating ferroptosis, such as Decr2, determine tumor sensitivity to immunotherapy [329]. Several nano-enabled immunotherapy platforms have demonstrated that inducing cuproptosis can reshape the TME and potentiate PD-L1 blockade, even in resistant cancers [333, 334]. Additionally, dual ferroptosis-cuproptosis platforms, such as AuBiCu-PEG NPs, have been used to amplify RT and immunotherapy responses, overcome PD-L1 upregulation, and enhance systemic immunity [335]. More recently, evidence suggests that CAR-NK cells may also induce ferroptosis through the release of IFN-γ and ROS, particularly when targeting PSMA-positive solid tumors. For instance, PSMA is highly expressed in PCa cells, and the emerging PSMA-targeted immune strategy offers the advantages of high specificity and efficiency in treating PCa. Combined treatment with anti-PSMA CAR-NK cells and anti-PD-L1 monoclonal antibody enhances the effectiveness of antitumor therapy against CRPC. The CAR-NK92MI cells against PSMA-targeted polypeptide selectively killed PSMA-positive C4-2 cells through IFN-γ-mediated ferroptosis [279, 336]. This mode of cell death can bypass classical apoptosis resistance and contribute to antitumor immunity [337]. Additionally, memory-like CAR-NK cells, induced by IL-12/15/18 activation, exhibit enhanced persistence and killing capacity against resistant cancer types, suggesting a potential role in durable tumor control [338].

4.3 | Targeting Cell Death in RT

RT remains a cornerstone of cancer treatment and is increasingly understood not only as a DNA-damaging therapy but also as a modulator of PCD. Its therapeutic efficacy largely depends on its ability to activate intrinsic and extrinsic death pathways in tumor cells. Apoptosis is the primary mechanism through which RT exerts its cytotoxic effects. Radiation-induced DNA damage activates p53-related pathways that culminate in MOMP and caspase-8 activation [339]. However, mutations in apoptosis regulators such as TP53 or BCL2 often confer resistance to apoptosis, prompting the need to target alternative PCD pathways. Radiation can trigger pyroptosis through caspase-1 or -3 activation, resulting in enhanced antitumor immunity via cytokine release and immune cell recruitment [340]. Harnessing pyroptosis may not only potentiate tumor clearance but also mitigate resistance observed in apoptosis-impaired cancers. It is noteworthy that RT-induced apoptosis in immune cells may cause clinical side effects of the treatment [341]. RT also modulates autophagy, which serves a protective function in PCa under radiation therapy. Overexpression of LC3A provides a functional survival mechanism for PCa cells in response to RT by activating autophagy [342]. While autophagy may initially protect cancer cells by clearing damaged organelles, excessive autophagy can lead to type II PCD. Combining RT with autophagy inhibitors (e.g., chloroquine) has shown promise in enhancing radiosensitivity in glioblastoma and pancreatic cancer [343].

RT increases ROS and depletes GSH, making cancer cells susceptible to metal ion-dependent PCD. The key regulators of ferroptosis, such as GPX4 and SLC7A11, are downregulated by ionizing radiation, sensitizing tumor cells to ferroptosis and promoting tumor regression [194]. It has also been shown to enhance cellular Cu uptake and oxidative stress, thereby potentially priming cells for cuproptosis [318]. Besides, emerging findings indicate that ferroptosis-related molecules may act as markers for predicting radiosensitivity and PCD in PCa [344, 345]. Moreover, these pathways contribute to RT-induced ICD. The release of oxidized lipids, mitochondrial DAMPs, and proinflammatory cytokines from ferroptotic and cuproptotic cells can enhance dendritic cell activation and T-cell recruitment, suggesting a role for metal-dependent death in the abscopal effect and immune priming [346]. RT not only kills tumor cells directly but also acts as an immunogenic trigger, shaping the TME through PCD-induced immunostimulatory effects. This is exemplified by the enhanced efficacy of combining RT with PD-1/PD-L1 ICIs. Several studies have shown that RT upregulates PD-L1 expression on tumor cells, and its blockade synergizes with radiation to enhance tumor antigen presentation and T-cell activation [347, 348].

4.4 | Targeting Cell Death in Targeted Therapy

Targeted therapy has revolutionized cancer treatment by selectively inhibiting molecular pathways essential for tumor survival

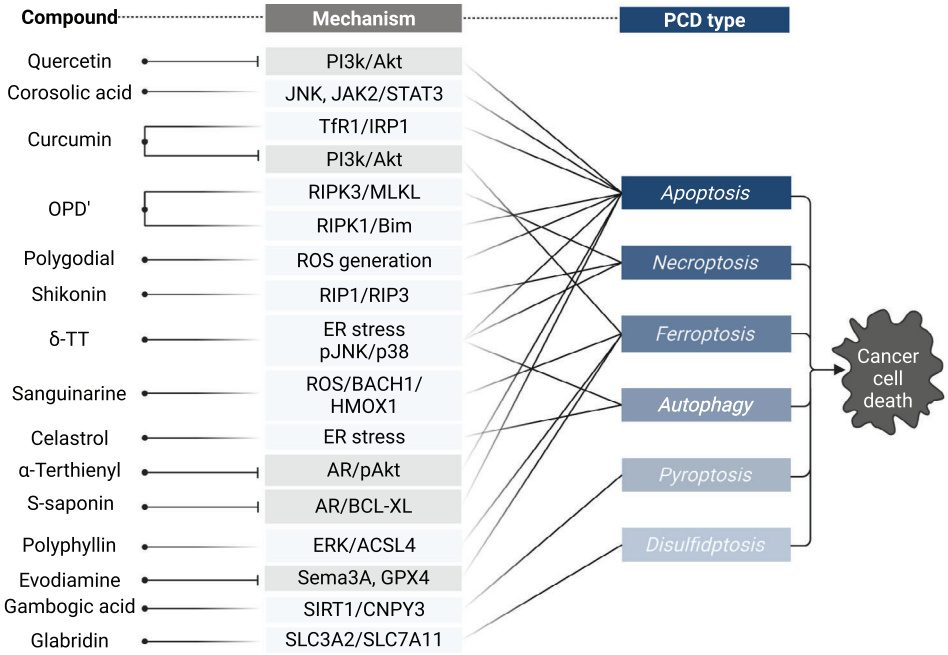


FIGURE 4 | Representative natural compounds that target PCD for the treatment of cancer. Numerous natural products and bioactive components derived from TCM have been reported to exhibit antitumor effects by inducing PCD. Here, we summarize representative compounds targeting specific PCD modalities, along with their molecular mechanisms, to demonstrate the potential of PCD modulation in natural product-based cancer therapy. *Abbreviation*: TCM: traditional Chinese medicine.

and proliferation [190]. Beyond cytostatic effects, increasing evidence shows that many targeted agents exert therapeutic efficacy by engaging PCD pathways, including apoptosis, ferroptosis, cuproptosis, and emerging modalities such as disulfidptosis and entosis. TKIs targeting EGFR, ALK, or KRAS not only inhibit mitogenic signaling but also activate apoptosis and pyroptosis, as shown by gasdermin-mediated membrane permeabilization following caspase-3 activation [349]. Venetoclax, a BCL-2 inhibitor approved for chronic lymphocytic leukemia, reinstates the mitochondrial apoptosis pathway by antagonizing antiapoptotic proteins [350].

In recent years, targeting ferroptosis has represented a significant focus of small-molecule drug discovery. Compounds like erastin, RSL3, sulfasalazine, and sorafenib deplete intracellular GSH or inhibit GPX4, leading to ROS accumulation and ferroptotic death [351]. Novel molecules such as MESA (a morpholine derivative) specifically target the Nrf2 pathway, sensitizing prostate and ovarian cancer cells to ferroptosis via GPX4 downregulation and Fe overload [352]. Other compounds like Compound 8 inhibit the xCT transporter (SLC7A11), depleting GSH and triggering ferroptosis, and show enhanced activity compared with classical inducers [353]. Small-molecule ferroptosis inducers are now being engineered to specifically target CSCs, with evidence that certain ROS-inducing compounds exhibit higher toxicity against mesenchymal BCa subpopulations [354]. Moreover, strategies that transition ferroptosis to apoptosis by transcriptional reprogramming or small molecule cocktails are being explored to enhance therapeutic outcomes and avoid resistance [355]. Adding to this repertoire, disulfidptosis, a newly identified death form triggered by disulfide stress under glucose starvation, is being targeted by small molecules that inhibit GLUT1 or exacerbate ER stress [356], offering unique therapeutic entry points, especially in tumors with high SLC7A11 expression. Taken together, these examples underscore that modern targeted therapy is no longer limited to growth inhibition. Rather, it increasingly seeks to orchestrate selective PCD engagement using pharmacologically refined small molecules, providing new therapeutic angles to tackle apoptosis resistance, metabolic rewiring, and tumor heterogeneity.

4.5 | Targeting Cell Death in Hormone Therapy

Endocrine or hormone therapy plays a central role in the treatment of hormone-driven malignancies such as BCa, EC, and PCa, where therapeutic strategies typically aim to suppress ER or AR signaling. However, treatment resistance frequently arises, which is often mediated by impaired cell death responses. Increasing evidence reveals that manipulation of PCD can sensitize hormone-refractory tumors and augment therapeutic efficacy. In androgen deprivation therapy (ADT)-resistant PCa, which is CRPC, targeting lipid metabolism regulators such as PHGDH, DECR1, and MBOAT1/2 restores ferroptosis susceptibility and enhances antitumor responses. Inhibition of these enzymes leads to Fe-dependent lipid peroxidation and cell death even in the presence of AR signaling [357], suggesting a promising route for next-generation ADT. The impact of autophagy on ADT is a subject of ongoing investigation. In the context of ADT-induced energy deficiency, AMPK is activated and triggers autophagy, which provides an apparent survival advantage for PCa cells [358]. Despite the dual nature of autophagy, its stimulation by ADT tends to negatively affect tumor growth. Inhibition of autophagy has been proposed to enhance the effectiveness of combined androgen ablation and chemotherapy [359], and it is also considered a strategy to boost the efficacy of abiraterone in

TABLE 3 | Representative clinical trials of anticancer treatment targeting PCD.

Drug/treatment	PCD type	Cancer type	NCT number
Quercetin + dasatinib	Apoptosis	Breast cancer Prostate cancer Multiple myeloma	NCT06355037 NCT01538316 NCT01912820 NCT06940297
NKG2D-CAR T cells	Apoptosis	Colorectal cancer Gastric cancer Liver cancer Prostate cancer Sarcoma	NCT04107142 NCT05248048 NCT06087341 NCT05382377
δ-TT/γ-TT	Apoptosis, autophagy	Breast cancer Prostate cancer Pancreatic cancer	NCT00844792 NCT01571921 NCT00985777
Selenium	Apoptosis, necroptosis	Lung cancer Bladder cancer Prostate cancer	NCT00008385 NCT00729287 NCT00030901 NCT00022165 NCT01155791
Curcumin	Apoptosis, autophagy Ferroptosis	Breast cancer Colorectal cancer Pancreatic cancer Pediatric cancer Prostate cancer Head and neck cancer	NCT03980509 NCT00027495 NCT00094445 NCT06044142 NCT02064673 NCT04208334
BI2536	Necroptosis	Breast cancer Endometrial cancer Lung cancer Pancreatic cancer Prostate cancer Lymphoma	NCT00526149 NCT00376623 NCT00710710 NCT00706498 NCT00243087
Photodynamic therapy	Necroptosis, autophagy	Bile duct cancer Cervical cancer Esophageal cancer Oral cancer Prostate cancer	NCT00005067 NCT02304770 NCT01755013 NCT03638622 NCT01043016
SMAC mimetics	Necroptosis	Lung cancer Multiple myeloma	NCT03270176 NCT01955434 NCT03111992
Iron nanoparticles	Ferroptosis	Breast cancer Cervical cancer Colorectal cancer Liver cancer Lymphoma	NCT06048367 NCT04682847 NCT06048367 NCT01815333
Statins	Ferroptosis	Breast cancer Pancreatic cancer Prostate cancer	NCT00816244 NCT03454529 NCT06241352 NCT01759836
Elesclomol (STA-4783)	Cuproptosis	Epithelial cancer Kidney cancer Lung cancer Prostate cancer	NCT00888615 NCT00088088 NCT00808418

(Continues)

TABLE 3 | (Continued)

Drug/treatment	PCD type	Cancer type	NCT number
Onvansertib	Entosis	Colorectal cancer	NCT05593328
		Pancreatic cancer	NCT04752696
		Prostate cancer	NCT03414034
		Acute myeloid leukemia	NCT03303339
Nintedanib (BIBF 1120)	Entosis	Cervical cancer	NCT02009579
		Lung cancer	NCT01948141
		Ovarian cancer	NCT00710762
		Prostate cancer	NCT02182219

Note: Data were acquired from NIH-ClinicalTrials.gov (https://clinicaltrials.gov/).

CRPC [360]. Recent findings suggest that high-dose androgen dihydrotestosterone (DHT) can induce autophagy and cell death in enzalutamide-resistant PCa [253]. SIRT1, a vital regulator of autophagy in PCa, might be a potential parallel target of ADT therapy. Its inhibition can amplify the effects of enzalutamide and abiraterone on PCa [83].

In hormone receptor-positive BCa, autophagy appears to mediate resistance to antiestrogen agents like tamoxifen or aromatase inhibitors. Metronomic chemotherapy combined with endocrine therapy (e.g., cyclophosphamide and letrozole) has shown improved outcomes, in part by reactivating apoptotic pathways, as well as inducing autophagy-related stress that promotes cell vulnerability [361]. The GPX4-independent regulation of ferroptosis by sex hormone receptors (e.g., ER, AR) demonstrates its significant potential in influencing hormone-dependent cancers [357]. In EC, a prototypical hormone-driven tumor, recent studies underscore the relevance of cell death regulation in the efficacy of endocrine therapy. Gonadotropin-releasing hormone (GnRH) analogs, including agonists and antagonists, have been shown to directly inhibit EC cell proliferation via activation of apoptotic pathways, such as MAPK–GADD45α signaling, caspase-3 cleavage, and PKCδ–p53/p21 cascade activation [362, 363]. Furthermore, ferroptosis and cuproptosis have emerged as promising avenues in EC research. Transcriptomic and clinical analyses have identified ferroptosis-related gene signatures and long noncoding RNAs that predict prognosis and immune landscape, supporting the feasibility of ferroptosis-guided precision endocrine therapy [364, 365]. Finally, natural products are also emerging approaches for cancer treatment that target different PCDs (Figure 4).

For the clinical application, several of the mentioned compounds have already undergone clinical trials in solid tumors [124, 366, 367]. As mechanistic research into PCD-based treatments expands and clinical practices increase, the landscape of cancer therapy is poised for significant evolution. We summarized representative clinical trials in Table 3, and more comprehensive information can be referred to the online clinical research study database "Clinicaltrials.gov."

5 | Conclusion and Perspective

Therapeutic approaches targeting PCD have quickly gained traction as a promising direction in cancer treatment. Traditional strategies like chemotherapy, RT, and some targeted therapies primarily aim to induce apoptosis. However, resistance to apoptosis, especially in advanced or treatment-resistant tumors, remains a major hurdle that often leads to poor clinical outcomes. To address this, newer forms of PCD such as ferroptosis, pyroptosis, and cuproptosis are being explored as alternative methods to eliminate cancer cells and bypass resistance pathways. Recent studies emphasize the potential benefits of incorporating these nonapoptotic death pathways into cancer therapy. For instance, inducers of ferroptosis have demonstrated effectiveness in preclinical models of therapy-resistant cancers, including breast, prostate, and pancreatic malignancies. Likewise, triggering PANoptosis could amplify both immune system responses and direct tumor cell killing [14, 17].

Despite these advances, significant challenges persist. These include risks related to unintended toxicity, variable responses depending on the tumor context, and a still-evolving understanding of how different cell death mechanisms interact. Moving forward, it will be essential to map out the intricate relationships among various PCD pathways in the tumor. Combination strategies, like pairing ferroptosis activators with immune checkpoint blockade or targeting molecules that regulate multiple PCD types, might offer more robust outcomes while avoiding resistance loops. At the same time, leveraging specific metabolic or genetic traits unique to tumors will be key to ensuring precise and selective activation of cell death.

Building on the existing crosstalk among various forms of PCD, advanced CRISPR-based technologies offer a powerful platform to identify key molecular mediators that orchestrate the interplay between different PCD pathways [368]. By strategically activating multiple PCD mechanisms, this approach holds promise in overcoming resistance to a single mode of cell death. Emerging technologies, such as single-cell RNA sequencing and spatial transcriptomics, are likely to accelerate the discovery of biomarkers that can guide these approaches. Ultimately, the success of PCD-centered therapies may rely on developing precision models that customize treatment based on the unique PCD profiles of individuals. As our knowledge base expands and more therapies progress from lab to clinic, these strategies hold the potential to reshape how we treat cancer, offering renewed hope in the fight against therapeutic resistance and improving long-term patient outcomes.

Author Contributions

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

References

1. G. S. Kopeina and B. Zhivotovsky, "Programmed Cell Death: Past, Present and Future," *Biochemical and Biophysical Research Communications* 633 (2022): 55–58.

2. L. Galluzzi, I. Vitale, S. A. Aaronson, et al., "Molecular Mechanisms of Cell Death: Recommendations of the Nomenclature Committee on Cell Death," *Cell Death and Differentiation* 25, no. 3 (2018): 486–541.

3. P. Tsvetkov, S. Coy, B. Petrova, et al., "Copper Induces Cell Death by Targeting Lipoylated TCA Cycle Proteins," *Science* 375, no. 6586 (2022): 1254–1261.

4. W. Fu, J. Wang, T. Li, et al., "Persistent Activation of TRPM4 Triggers Necrotic Cell Death Characterized by Sodium Overload," *Nature Chemical Biology* 21, no. 8 (2025): 1238–1249.

5. X. Liu, L. Nie, Y. Zhang, et al., "Actin Cytoskeleton Vulnerability to Disulfide Stress Mediates Disulfidptosis," *Nature Cell Biology* 25, no. 3 (2023): 404–414.

6. J. Yuan and D. Ofengeim, "A Guide to Cell Death Pathways," *Nature Reviews Molecular Cell Biology* 25, no. 5 (2024): 379–395.

7. S. K. Yu, J. Yang, Q. Zhang, T. Yu, and K. H. Lu, "A Novel Signature Based on Twelve Programmed Cell Death Patterns to Predict the Prognosis of Lung Adenocarcinoma," *American Journal of Translational Research* 16, no. 5 (2024): 2082–2102.

8. L. Zhang and M. Peng, "Integrated Bioinformatic Analysis Identified a Novel Prognostic Pan-programmed Cell Death Signature for Bladder Cancer," *Frontiers in Immunology* 13 (2022): 1030097.

9. S. Bedoui, M. J. Herold, and A. Strasser, "Emerging Connectivity of Programmed Cell Death Pathways and Its Physiological Implications," *Nature Reviews Molecular Cell Biology* 21, no. 11 (2020): 678–695.

10. M. Wang, F. Yu, Y. Zhang, and P. Li, "Programmed Cell Death in Tumor Immunity: Mechanistic Insights and Clinical Implications," *Frontiers in Immunology* 14 (2023): 1309635.

11. A. P. Mishra, B. Salehi, M. Sharifi-Rad, et al., "Programmed Cell Death, From a Cancer Perspective: An Overview," *Molecular Diagnosis & Therapy* 22, no. 3 (2018): 281–295.

12. K. Cao, J. Zhu, M. Lu, et al., "Analysis of Multiple Programmed Cell Death-related Prognostic Genes and Functional Validations of Necroptosis-associated Genes in Oesophageal Squamous Cell Carcinoma," *EBioMedicine* 99 (2024): 104920.

13. J. Gao, A. Xiong, J. Liu, et al., "PANoptosis: Bridging Apoptosis, Pyroptosis, and Necroptosis in Cancer Progression and Treatment," *Cancer Gene Therapy* 31, no. 7 (2024): 970–983.

14. S. Maitra, D. Bhattacharya, S. Paul, et al., "Programmed Cell Death Protein 1 (PD-1) in Relation to PANoptosis: Immune Pharmacological Targets for Management of Breast Adenocarcinoma," *Endocrine, Metabolic & Immune Disorders Drug Targets* 23, no. 13 (2023): 1571–1585.

15. H. Li, Y. Sun, Y. Yao, et al., "USP8-governed GPX4 Homeostasis Orchestrates Ferroptosis and Cancer Immunotherapy," *PNAS* 121, no. 16 (2024): e2315541121.

16. F. Yang, Y. Xiao, J. H. Ding, et al., "Ferroptosis Heterogeneity in Triple-negative Breast Cancer Reveals an Innovative Immunotherapy Combination Strategy," *Cell Metabolism* 35, no. 1 (2023): 84–100.e108.

17. L. Zhao, X. Zhou, F. Xie, et al., "Ferroptosis in Cancer and Cancer Immunotherapy," *Cancer communications (London)* 42, no. 2 (2022): 88–116.

18. M. Wu, Q. Huang, Y. Xie, et al., "Improvement of the Anticancer Efficacy of PD-1/PD-L1 Blockade via Combination Therapy and PD-L1 Regulation," *Journal of Hematology & Oncology* 15, no. 1 (2022): 24.

19. Y. Zhang and Z. Zhang, "The History and Advances in Cancer Immunotherapy: Understanding the Characteristics of Tumor-infiltrating Immune Cells and Their Therapeutic Implications," *Cellular & Molecular Immunology* 17, no. 8 (2020): 807–821.

20. K. Hänggi and B. Ruffell, "Cell Death, Therapeutics, and the Immune Response in Cancer," *Trends in Cancer* 9, no. 5 (2023): 381–396.

21. X. Chen, R. Kang, G. Kroemer, and D. Tang, "Broadening Horizons: The Role of Ferroptosis in Cancer," *Nature Reviews Clinical Oncology* 18, no. 5 (2021): 280–296.

22. Z. Su, Z. Yang, Y. Xu, Y. Chen, and Q. Yu, "Apoptosis, Autophagy, Necroptosis, and Cancer Metastasis," *Molecular Cancer* 14 (2015): 48.

23. P. R. Nepali and N. Kyprianou, "Anoikis in Phenotypic Reprogramming of the Prostate Tumor Microenvironment," *Frontiers in Endocrinology (Lausanne)* 14 (2023): 1160267.

24. J. Song, R. Xu, H. Zhang, et al., "Cell-in-Cell-Mediated Entosis Reveals a Progressive Mechanism in Pancreatic Cancer," *Gastroenterology* 165, no. 6 (2023): 1505–1521.e1520.

25. S. K. Hsu, C. Y. Li, I. L. Lin, et al., "Inflammation-related Pyroptosis, a Novel Programmed Cell Death Pathway, and Its Crosstalk With Immune Therapy in Cancer Treatment," *Theranostics* 11, no. 18 (2021): 8813–8835.

26. Y. Zhou, L. Liu, S. Tao, et al., "Parthanatos and Its Associated Components: Promising Therapeutic Targets for Cancer," *Pharmacological Research* 163 (2021): 105299.

27. P. Zheng, C. Zhou, Y. Ding, and S. Duan, "Disulfidptosis: A New Target for Metabolic Cancer Therapy," *Journal of Experimental & Clinical Cancer Research* 42, no. 1 (2023): 103.

28. D. Tang, G. Kroemer, and R. Kang, "Targeting Cuproplasia and Cuproptosis in Cancer," *Nature Reviews Clinical Oncology* 21, no. 5 (2024): 370–388.

29. J. F. Kerr, A. H. Wyllie, and A. R. Currie, "Apoptosis: A Basic Biological Phenomenon With Wide-ranging Implications in Tissue Kinetics," *British Journal of Cancer* 26, no. 4 (1972): 239–257.

30. X. Xu, Y. Lai, and Z. C. Hua, "Apoptosis and Apoptotic Body: Disease Message and Therapeutic Target Potentials," *Bioscience Reports* 39, no. 1 (2019): BSR20180992.

31. J. F. Kerr and J. Searle, "Deletion of Cells by Apoptosis During Castration-induced Involution of the Rat Prostate," *Virchows Archiv B: Cell Pathology* 13, no. 2 (1973): 87–102.

32. J. Searle, D. J. Collins, B. Harmon, and J. F. Kerr, "The Spontaneous Occurrence of Apoptosis in Squamous Carcinomas of the Uterine Cervix," *Pathology* 5, no. 2 (1973): 163–169.

33. A. Young, W. Bu, W. Jiang, et al., "Targeting the Pro-survival Protein BCL-2 to Prevent Breast Cancer," *Cancer Prevention Research (Philadelphia, Pa)* 15, no. 1 (2022): 3–10.

34. Y. G. Lee, P. Guruprasad, G. Ghilardi, et al., "Modulation of BCL-2 in both T Cells and Tumor Cells to Enhance Chimeric Antigen Receptor T-cell Immunotherapy Against Cancer," *Cancer Discovery* 12, no. 10 (2022): 2372–2391.

35. S. Chen, Y. Ren, and P. Duan, "Biomimetic Nanoparticle Loading Obatoclax Mesylate for the Treatment of Non-small-cell Lung Cancer (NSCLC) Through Suppressing Bcl-2 Signaling," *Biomedicine & Pharmacotherapy* 129 (2020): 110371.

36. J. Sun, J. Piao, N. Li, Y. Yang, K. Y. Kim, and Z. Lin, "Valproic Acid Targets HDAC1/2 and HDAC1/PTEN/Akt Signalling to Inhibit Cell Proliferation via the Induction of Autophagy in Gastric Cancer," *The FEBS Journal* 287, no. 10 (2020): 2118–2133.

37. A. M. Pesch, B. C. Chandler, A. R. Michmerhuizen, et al., "Bcl-xL Inhibition Radiosensitizes PIK3CA/PTEN Wild-type Triple Negative Breast Cancers With Low Mcl-1 Expression," *Cancer Research Communications* 2, no. 7 (2022): 679–693.

38. I. Guccini, A. Revandkar, M. D'Ambrosio, et al., "Senescence Reprogramming by TIMP1 Deficiency Promotes Prostate Cancer Metastasis," *Cancer Cell* 39, no. 1 (2021): 68–82.e69.

39. L. Trabzonlu, I. Kulac, Q. Zheng, et al., "Molecular Pathology of High-Grade Prostatic Intraepithelial Neoplasia: Challenges and Opportunities," *Cold Spring Harbor Perspectives in Medicine* 9, no. 4 (2019): a030403.

40. M. C. Haffner and C. E. Barbieri, "Shifting Paradigms for High-grade Prostatic Intraepithelial Neoplasia," *European Urology* 69, no. 5 (2016): 831–833.

41. M. I. Johnson, M. C. Robinson, C. Marsh, C. N. Robson, D. E. Neal, and F. C. Hamdy, "Expression of Bcl-2, Bax, and p53 in High-grade Prostatic Intraepithelial Neoplasia and Localized Prostate Cancer: Relationship With Apoptosis and Proliferation," *Prostate* 37, no. 4 (1998): 223–229.

42. S. Baspinar, S. Bircan, H. Orhan, N. Kapucuoglu, and K. K. Bozkurt, "The Relation of Beclin 1 and Bcl-2 Expressions in High Grade Prostatic Intraepithelial Neoplasia and Prostate Adenocarcinoma: A Tissue Microarray Study," *Pathology, Research and Practice* 210, no. 7 (2014): 412–418.

43. D. A. Bax, J. Haringsma, A. W. Einerhand, et al., "MUC4 is Increased in High Grade Intraepithelial Neoplasia in Barrett's Oesophagus and is Associated With a Proapoptotic Bax to Bcl-2 Ratio," *Journal of Clinical Pathology* 57, no. 12 (2004): 1267–1272.

44. V. R. Litle, J. D. Leavenworth, T. M. Darragh, et al., "Angiogenesis, Proliferation, and Apoptosis in Anal High-grade Squamous Intraepithelial Lesions," *Diseases of the Colon and Rectum* 43, no. 3 (2000): 346–352.

45. S. Heimer, G. Knoll, K. Schulze-Osthoff, and M. Ehrenschwender, "Raptinal Bypasses BAX, BAK, and BOK for Mitochondrial Outer Membrane Permeabilization and Intrinsic Apoptosis," *Cell Death & Disease* 10, no. 8 (2019): 556.

46. A. Safi, E. Heidarian, and R. Ahmadi, "Quercetin Synergistically Enhances the Anticancer Efficacy of Docetaxel Through Induction of Apoptosis and Modulation of PI3K/AKT, MAPK/ERK, and JAK/STAT3 Signaling Pathways in MDA-MB-231 Breast Cancer Cell Line," *International Journal of Molecular and Cellular Medicine* 10, no. 1 (2021): 11–22.

47. S. Shukla, P. Fu, and S. Gupta, "Apigenin Induces Apoptosis by Targeting Inhibitor of Apoptosis Proteins and Ku70-Bax Interaction in Prostate Cancer," *Apoptosis* 19, no. 5 (2014): 883–894.

48. J. Duo, G. G. Ying, G. W. Wang, and L. Zhang, "Quercetin Inhibits human Breast Cancer Cell Proliferation and Induces Apoptosis via Bcl-2 and Bax Regulation," *Molecular Medicine Reports* 5, no. 6 (2012): 1453–1456.

49. S. von Karstedt, A. Montinaro, and H. Walczak, "Exploring the TRAILs Less Travelled: TRAIL in Cancer Biology and Therapy," *Nature Reviews Cancer* 17, no. 6 (2017): 352–366.

50. H. Lai, D. Zeng, C. Liu, Q. Zhang, X. Wang, and T. Chen, "Selenium-containing Ruthenium Complex Synergizes With Natural Killer Cells to Enhance Immunotherapy Against Prostate Cancer via Activating TRAIL/FasL Signaling," *Biomaterials* 219 (2019): 119377.

51. S. Y. Tung, K. C. Lee, K. F. Lee, et al., "Apoptotic Mechanisms of Gastric Cancer Cells Induced by Isolated Erinacine S Through Epigenetic Histone H3 Methylation of FasL and TRAIL," *Food & Function* 12, no. 8 (2021): 3455–3468.

52. A. Rossin, G. Miloro, and A. O. Hueber, "TRAIL and FasL Functions in Cancer and Autoimmune Diseases: Towards an Increasing Complexity," *Cancers (Basel)* 11, no. 5 (2019): 639.

53. A. Degterev, Z. Huang, M. Boyce, et al., "Chemical Inhibitor of Nonapoptotic Cell Death With Therapeutic Potential for Ischemic Brain Injury," *Nature Chemical Biology* 1, no. 2 (2005): 112–119.

54. T. Vanden Berghe, A. Linkermann, S. Jouan-Lanhouet, H. Walczak, and P. Vandenabeele, "Regulated Necrosis: The Expanding Network of Non-apoptotic Cell Death Pathways," *Nature Reviews Molecular Cell Biology* 15, no. 2 (2014): 135–147.

55. D. Ma, X. Wang, J. Liu, Y. Cui, S. Luo, and F. Wang, "The Development of Necroptosis: What We Can Learn," *Cell Stress & Chaperones* 28, no. 6 (2023): 969–987.

56. K. Ye, Z. Chen, and Y. Xu, "The Double-edged Functions of Necroptosis," *Cell Death & Disease* 14, no. 2 (2023): 163.

57. P. Lin, C. Lin, R. He, et al., "TRAF6 regulates the Abundance of RIPK1 and Inhibits the RIPK1/RIPK3/MLKL Necroptosis Signaling Pathway and Affects the Progression of Colorectal Cancer," *Cell Death & Disease* 14, no. 1 (2023): 6.

58. C. C. Lin, N. W. Mabe, Y. T. Lin, et al., "RIPK3 upregulation Confers Robust Proliferation and Collateral Cystine-dependence on Breast Cancer Recurrence," *Cell Death and Differentiation* 27, no. 7 (2020): 2234–2247.

59. L. Jing, M. E. Zhai, J. Cui, et al., "CNOT3 contributes to Cisplatin Resistance in Lung Cancer Through Inhibiting RIPK3 Expression," *Apoptosis* 24, no. 7-8 (2019): 673–685.

60. R. Karlowitz and S. J. L. van Wijk, "Surviving Death: Emerging Concepts of RIPK3 and MLKL Ubiquitination in the Regulation of Necroptosis," *The FEBS Journal* 290, no. 1 (2023): 37–54.

61. Y. Tan, E. Sementino, M. Cheung, et al., "Somatic Epigenetic Silencing of RIPK3 Inactivates Necroptosis and Contributes to Chemoresistance in Malignant Mesothelioma," *Clinical Cancer Research* 27, no. 4 (2021): 1200–1213.

62. X. Guo, R. Li, J. Cui, et al., "Induction of RIPK3/MLKL-mediated Necroptosis by Erigeron Breviscapus Injection Exhibits Potent Antitumor Effect," *Frontiers in Pharmacology* 14 (2023): 1219362.

63. Y. Liu, H. Wei, and J. Li, "A Review on SIRT3 and Its Natural Small Molecule Activators as a Potential Preventive and Therapeutic Target," *European Journal of Pharmacology* 963 (2024): 176155.

64. N. D'Onofrio, E. Martino, A. Balestrieri, et al., "Diet-derived Ergothioneine Induces Necroptosis in Colorectal Cancer Cells by Activating the SIRT3/MLKL Pathway," *The FEBS Letters* 596, no. 10 (2022): 1313–1329.

65. W. Fu, H. Li, H. Fu, et al., "The SIRT3 and SIRT6 Promote Prostate Cancer Progression by Inhibiting Necroptosis-Mediated Innate Immune Response," *Journal of Immunology Research* 2020 (2020): 8820355.

66. X. Tang, Y. Li, L. Liu, et al., "Sirtuin 3 Induces Apoptosis and Necroptosis by Regulating Mutant p53 Expression in Small-Cell Lung Cancer," *Oncology Reports* 43, no. 2 (2020): 591–600.

67. X. Liu, N. Zhang, D. Wang, et al., "Downregulation of Reticulocalbin-1 Differentially Facilitates Apoptosis and Necroptosis in human Prostate Cancer Cells," *Cancer Science* 109, no. 4 (2018): 1147–1157.

68. R. Karki, B. Sundaram, B. R. Sharma, et al., "ADAR1 restricts ZBP1-mediated Immune Response and PANoptosis to Promote Tumorigenesis," *Cell Reports* 37, no. 3 (2021): 109858.

69. M. Zheng and T. D. Kanneganti, "The Regulation of the ZBP1-NLRP3 Inflammasome and Its Implications in Pyroptosis, Apoptosis, and Necroptosis (PANoptosis)," *Immunological Reviews* 297, no. 1 (2020): 26–38.

70. N. Mizushima and M. Komatsu, "Autophagy: Renovation of Cells and Tissues," *Cell* 147, no. 4 (2011): 728–741.

71. J. D. Mancias and A. C. Kimmelman, "Mechanisms of Selective Autophagy in Normal Physiology and Cancer," *Journal of Molecular Biology* 428, no. 9 Pt A (2016): 1659–1680.

72. S. S. Singh, S. Vats, A. Y. Chia, et al., "Dual Role of Autophagy in Hallmarks of Cancer," *Oncogene* 37, no. 9 (2018): 1142–1158.

73. S. Liu, S. Yao, H. Yang, S. Liu, and Y. Wang, "Autophagy: Regulator of Cell Death," *Cell Death & Disease* 14, no. 10 (2023): 648.

74. J. Liu, Y. Liu, Y. Wang, et al., "TMEM164 is a New Determinant of Autophagy-dependent Ferroptosis," *Autophagy* 19, no. 3 (2023): 945–956.

75. F. Chen, X. Cai, R. Kang, J. Liu, and D. Tang, "Autophagy-Dependent Ferroptosis in Cancer," *Antioxid Redox Signaling* 39, no. 1-3 (2023): 79–101.

76. B. Zhou, J. Liu, R. Kang, D. J. Klionsky, G. Kroemer, and D. Tang, "Ferroptosis Is a Type of Autophagy-dependent Cell Death," *Seminars in Cancer Biology* 66 (2020): 89–100.

77. J. Debnath, N. Gammoh, and K. M. Ryan, "Autophagy and Autophagy-related Pathways in Cancer," *Nature Reviews Molecular Cell Biology* 24, no. 8 (2023): 560–575.

78. L. Polletta, E. Vernucci, I. Carnevale, et al., "SIRT5 regulation of Ammonia-induced Autophagy and Mitophagy," *Autophagy* 11, no. 2 (2015): 253–270.

79. Z. Deng, M. Sun, J. Wu, et al., "SIRT1 attenuates sepsis-induced Acute Kidney Injury via Beclin1 Deacetylation-mediated Autophagy Activation," *Cell Death & Disease* 12, no. 2 (2021): 217.

80. J. Li, H. Zhan, Y. Ren, et al., "Sirtuin 4 Activates Autophagy and Inhibits Tumorigenesis by Upregulating the p53 Signaling Pathway," *Cell Death and Differentiation* 30, no. 2 (2023): 313–326.

81. X. Wei, X. Xiong, P. Wang, S. Zhang, and D. Peng, "SIRT1-mediated Deacetylation of FOXO3 Enhances Mitophagy and Drives Hormone Resistance in Endometrial Cancer," *Molecular Medicine* 30, no. 1 (2024): 147.

82. H. Guo, H. Ding, X. Tang, et al., "Quercetin Induces Pro-apoptotic Autophagy via SIRT1/AMPK Signaling Pathway in human Lung Cancer Cell Lines A549 and H1299 in Vitro," *Thoracic Cancer* 12, no. 9 (2021): 1415–1422.

83. M. J. Powell, M. C. Casimiro, C. Cordon-Cardo, et al., "Disruption of a Sirt1-dependent Autophagy Checkpoint in the Prostate Results in Prostatic Intraepithelial Neoplasia Lesion Formation," *Cancer Research* 71, no. 3 (2011): 964–975.

84. S. Yi, B. Zheng, Y. Zhu, Y. Cai, H. Sun, and J. Zhou, "Melatonin Ameliorates Excessive PINK1/Parkin-mediated Mitophagy by Enhancing SIRT1 Expression in Granulosa Cells of PCOS," *American Journal of Physiology. Endocrinology and Metabolism* 319, no. 1 (2020): e91–e101.

85. J. Yao, J. Wang, Y. Xu, et al., "CDK9 inhibition Blocks the Initiation of PINK1-PRKN-mediated Mitophagy by Regulating the SIRT1-FOXO3-BNIP3 Axis and Enhances the Therapeutic Effects Involving Mitochondrial Dysfunction in Hepatocellular Carcinoma," *Autophagy* 18, no. 8 (2022): 1879–1897.

86. X. Wang, F. Xu, H. Kou, et al., "Stromal Cell-derived Small Extracellular Vesicles Enhance Radioresistance of Prostate Cancer Cells via Interleukin-8-induced Autophagy," *Journal of Extracellular Vesicles* 12, no. 7 (2023): e12342.

87. L. Yin, Y. Ye, L. Zou, et al., "AR Antagonists Develop Drug Resistance Through TOMM20 Autophagic Degradation-promoted Transformation to Neuroendocrine Prostate Cancer," *Journal of Experimental & Clinical Cancer Research* 42, no. 1 (2023): 204.

88. Y. Wang, N. Wu, J. Li, et al., "YAP1 Regulates the YAP1/AR/PSA Axis Through Autophagy in Castration-Resistant Prostate Cancer and Mediates T-Cell Immune and Inflammatory Cytokine Infiltration," *Biomedicines* 12, no. 3 (2024): 661.

89. J. Chen, F. Wang, H. Xu, et al., "Long Non-Coding RNA SNHG1 Regulates the Wnt/β-Catenin and PI3K/AKT/mTOR Signaling Pathways via EZH2 to Affect the Proliferation, Apoptosis, and Autophagy of Prostate Cancer Cell," *Frontiers in Oncology* 10 (2020): 552907.

90. Y. Yu, Y. Song, L. Cheng, et al., "CircCEMIP Promotes Anoikis-resistance by Enhancing Protective Autophagy in Prostate Cancer Cells," *Journal of Experimental & Clinical Cancer Research* 41, no. 1 (2022): 188.

91. Y. Yu, B. Liu, X. Li, et al., "ATF4/CEMIP/PKCα Promotes Anoikis Resistance by Enhancing Protective Autophagy in Prostate Cancer Cells," *Cell Death & Disease* 13, no. 1 (2022): 46.

92. R. K. S. Malireddi, S. Kesavardhana, and T. D. Kanneganti, "ZBP1 and TAK1: Master Regulators of NLRP3 Inflammasome/Pyroptosis, Apoptosis, and Necroptosis (PAN-optosis)," *Frontiers in Cellular and Infection Microbiology* 9 (2019): 406.

93. D. E. Place, S. Lee, and T. D. Kanneganti, "PANoptosis in Microbial Infection," *Current Opinion in Microbiology* 59 (2021): 42–49.

94. R. Karki, B. R. Sharma, E. Lee, et al., "Interferon Regulatory Factor 1 Regulates PANoptosis to Prevent Colorectal Cancer," *JCI Insight* 5, no. 12 (2020): e136720.

95. B. T. Cookson and M. A. Brennan, "Pro-inflammatory Programmed Cell Death," *Trends in Microbiology* 9, no. 3 (2001): 113–114.

96. K. Newton, V. M. Dixit, and N. Kayagaki, "Dying Cells Fan the Flames of Inflammation," *Science* 374, no. 6571 (2021): 1076–1080.

97. X. Lou, K. Li, B. Qian, Y. Li, D. Zhang, and W. Cui, "Pyroptosis Correlates With Tumor Immunity and Prognosis," *Communications Biology* 5, no. 1 (2022): 917.

98. J. B. Wang, Y. X. Gao, Y. H. Ye, et al., "Comprehensive Multi-omics Analysis of Pyroptosis for Optimizing Neoadjuvant Immunotherapy in Patients With Gastric Cancer," *Theranostics* 14, no. 7 (2024): 2915–2933.

99. X. Zhang, X. Wei, Y. Wang, et al., "Pyroptosis Regulators and Tumor Microenvironment Infiltration Characterization in Clear Cell Renal Cell Carcinoma," *Frontiers in Oncology* 11 (2021): 774279.

100. Z. Liu, S. Kuang, and Q. Chen, "A Review Focusing on the Role of Pyroptosis in Prostate Cancer," *Medicine* 102, no. 50 (2023): e36605.

101. Y. Ren, M. Feng, X. Hao, et al., "USP48 Stabilizes Gasdermin E to Promote Pyroptosis in Cancer," *Cancer Research* 83, no. 7 (2023): 1074–1093.

102. R. N. Zhang, Z. Q. Jing, L. Zhang, and Z. J. Sun, "Epigenetic Regulation of Pyroptosis in Cancer: Molecular Pathogenesis and Targeting Strategies," *Cancer Letters* 575 (2023): 216413.

103. Y. Zhang, J. Yang, Z. Wen, et al., "A Novel 3',5'-diprenylated Chalcone Induces Concurrent Apoptosis and GSDME-dependent Pyroptosis Through Activating PKCδ/JNK Signal in Prostate Cancer," *Aging (Albany NY)* 12, no. 10 (2020): 9103–9124.

104. A. Tian, T. Wu, Y. Zhang, J. Chen, J. Sha, and W. Xia, "Triggering Pyroptosis Enhances the Antitumor Efficacy of PARP Inhibitors in Prostate Cancer," *ellular Oncology (Dordr)* 46, no. 6 (2023): 1855–1870.

105. F. Wu, M. Wang, T. Zhong, et al., "Inhibition of CDC20 Potentiates Anti-tumor Immunity Through Facilitating GSDME-mediated Pyroptosis in Prostate Cancer," *Experimental Hematology & Oncology* 12, no. 1 (2023): 67.

106. A. El-Kenawi, A. Berglund, V. Estrella, et al., "Elevated Methionine Flux Drives Pyroptosis Evasion in Persister Cancer Cells," *Cancer Research* 83, no. 5 (2023): 720–734.

107. Y. Zeng, M. X. Li, S. Q. Wu, and C. Xu, "Carvedilol Induces Pyroptosis Through NLRP3-caspase1-ASC Inflammasome by Nuclear Migration of

NF-κB in Prostate Cancer Models," *Molecular Biology Reports* 51, no. 1 (2024): 201.

108. X. W. Zhang, L. Li, M. Liao, et al., "Thermal Proteome Profiling Strategy Identifies CNPY3 as a Cellular Target of Gambogic Acid for Inducing Prostate Cancer Pyroptosis," *Journal of Medicinal Chemistry* 67, no. 12 (2024): 10005–10011.

109. M. Overholtzer, A. A. Mailleux, G. Mouneimne, et al., "A Nonapoptotic Cell Death Process, Entosis, That Occurs by Cell-in-cell Invasion," *Cell* 131, no. 5 (2007): 966–979.

110. M. Kianfar, A. Balcerak, M. Chmielarczyk, L. Tarnowski, and E. A. Grzybowska, "Cell Death by Entosis: Triggers, Molecular Mechanisms and Clinical Significance," *International Journal of Molecular Sciences* 23, no. 9 (2022): 4985.

111. C. Zeng, B. Zeng, C. Dong, J. Liu, and F. Xing, "Rho-ROCK Signaling Mediates Entotic Cell Death in Tumor," *Cell Death Discovery* 6 (2020): 4.

112. J. Durgan, Y. Y. Tseng, J. C. Hamann, et al., "Mitosis Can Drive Cell Cannibalism Through Entosis," *Elife* 6 (2017): e27134.

113. J. Durgan and O. Florey, "Cancer Cell Cannibalism: Multiple Triggers Emerge for Entosis," *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research* 1865, no. 6 (2018): 831–841.

114. A. Hayashi, A. Yavas, C. A. McIntyre, et al., "Genetic and Clinical Correlates of Entosis in Pancreatic Ductal Adenocarcinoma," *Modern Pathology* 33, no. 9 (2020): 1822–1831.

115. S. Basbous, L. Dif, C. Dantzer, et al., "Loss of RND3/RHOE Controls Entosis Through LAMP1 Expression in Hepatocellular Carcinoma," *Cell Death & Disease* 15, no. 1 (2024): 46.

116. A. R. Lee and C. Y. Park, "Orai1 is an Entotic Ca(2+) Channel for Non-Apoptotic Cell Death, Entosis in Cancer Development," *Advanced Science (Weinh)* 10, no. 14 (2023): e2205913.

117. K. Gaptulbarova, I. A. Tsydenova, D. S. Dolgasheva, et al., "Mechanisms and Significance of Entosis for Tumour Growth and Progression," *Cell Death Discovery* 10, no. 1 (2024): 109.

118. E. Bozkurt, H. Düssmann, M. Salvucci, et al., "TRAIL Signaling Promotes Entosis in Colorectal Cancer," *Journal of Cell Biology* 220, no. 11 (2021): e202010030.

119. I. Dziuba, A. M. Gawel, P. Tyrna, et al., "Homotypic Entosis as a Potential Novel Diagnostic Marker in Breast Cancer," *International Journal of Molecular Sciences* 24, no. 7 (2023): 6819.

120. S. Wen, Z. Shang, S. Zhu, C. Chang, and Y. Niu, "Androgen Receptor Enhances Entosis, a Non-apoptotic Cell Death, Through Modulation of Rho/ROCK Pathway in Prostate Cancer Cells," *Prostate* 73, no. 12 (2013): 1306–1315.

121. J. Gilloteaux, C. Ruffo, J. M. Jamison, and J. L. Summers, "Modes of Internalizations of human Prostate Carcinoma (DU145) Cells in Vitro and in Murine Xenotransplants," *Ultrastructural Pathology* 40, no. 5 (2016): 231–239.

122. J. Balvan, J. Gumulec, M. Raudenska, et al., "Oxidative Stress Resistance in Metastatic Prostate Cancer: Renewal by Self-Eating," *PLoS ONE* 10, no. 12 (2015): e0145016.

123. J. Liu, L. Wang, Y. Zhang, et al., "Induction of Entosis in Prostate Cancer Cells by nintedanib and Its Therapeutic Implications," *Oncology Letters* 17, no. 3 (2019): 3151–3162.

124. J. C. Patterson, A. Varkaris, P. J. P. Croucher, et al., "Plk1 Inhibitors and Abiraterone Synergistically Disrupt Mitosis and Kill Cancer Cells of Disparate Origin Independently of Androgen Receptor Signaling," *Cancer Research* 83, no. 2 (2023): 219–238.

125. S. J. Dixon, K. M. Lemberg, M. R. Lamprecht, et al., "Ferroptosis: An Iron-dependent Form of Nonapoptotic Cell Death," *Cell* 149, no. 5 (2012): 1060–1072.

126. X. Jiang, B. R. Stockwell, and M. Conrad, "Ferroptosis: Mechanisms, Biology and Role in Disease," *Nature Reviews Molecular Cell Biology* 22, no. 4 (2021): 266–282.

127. K. Wu, M. Yan, T. Liu, et al., "Creatine Kinase B Suppresses Ferroptosis by Phosphorylating GPX4 Through a Moonlighting Function," *Nature Cell Biology* 25, no. 5 (2023): 714–725.

128. Y. He, W. Xu, Y. T. Xiao, H. Huang, D. Gu, and S. Ren, "Targeting Signaling Pathways in Prostate Cancer: Mechanisms and Clinical Trials," *Signal Transduction and Targeted Therapy* 7, no. 1 (2022): 198.

129. L. L. Sun, D. L. Linghu, and M. C. Hung, "Ferroptosis: A Promising Target for Cancer Immunotherapy," *American Journal of Cancer Research* 11, no. 12 (2021): 5856–5863.

130. Y. Liu, C. Duan, R. Dai, and Y. Zeng, "Ferroptosis-mediated Crosstalk in the Tumor Microenvironment Implicated in Cancer Progression and Therapy," *Frontiers in Cell and Developmental Biology* 9 (2021): 739392.

131. C. M. Bebber, F. Müller, L. Prieto Clemente, J. Weber, and S. von Karstedt, "Ferroptosis in Cancer Cell Biology," *Cancers (Basel)* 12, no. 1 (2020): 164.

132. M. J. Hangauer, V. S. Viswanathan, M. J. Ryan, et al., "Drug-tolerant Persister Cancer Cells Are Vulnerable to GPX4 Inhibition," *Nature* 551, no. 7679 (2017): 247–250.

133. V. S. Viswanathan, M. J. Ryan, H. D. Dhruv, et al., "Dependency of a Therapy-resistant state of Cancer Cells on a Lipid Peroxidase Pathway," *Nature* 547, no. 7664 (2017): 453–457.

134. L. Cheng, Q. He, B. Liu, et al., "SGK2 promotes Prostate Cancer Metastasis by Inhibiting Ferroptosis via Upregulating GPX4," *Cell Death & Disease* 14, no. 1 (2023): 74.

135. X. Zhao, T. Zhou, Y. Wang, et al., "Trigred Motif 36 Regulates Neuroendocrine Differentiation of Prostate Cancer via HK2 Ubiquitination and GPx4 Deficiency," *Cancer Science* 114, no. 6 (2023): 2445–2459.

136. J. Shi, C. Ma, Z. Zheng, et al., "Low-dose Antimony Exposure Promotes Prostate Cancer Proliferation by Inhibiting Ferroptosis via Activation of the Nrf2-SLC7A11-GPX4 Pathway," *Chemosphere* 339 (2023): 139716.

137. Z. Zhang, T. Xie, S. Zhang, et al., "Second Generation Androgen Receptor Antagonist, TQB3720 Abrogates Prostate Cancer Growth via AR/GPX4 Axis Activated Ferroptosis," *Frontiers in Pharmacology* 14 (2023): 1110146.

138. Y. Zhang, X. W. Song, N. Zhang, et al., "Ezetimibe Engineered L14-8 Suppresses Advanced Prostate Cancer by Activating PLK1/TP53-SAT1-Induced Ferroptosis," *Advanced Science (Weinheim, Baden-Wurttemberg, Germany)* 12, no. 29 (2025): e04192.

139. G. Li, Y. Yuan, X. Wu, and L. Wu, "Modulating NPC1L1 to Potentiate PARP Inhibitor-Induced Ferroptosis and Immune Response in Triple-Negative Breast Cancer," *Pharmaceutics* 17, no. 5 (2025): 554.

140. Q. Wang, S. Gao, Y. Shou, et al., "AIM2 promotes Renal Cell Carcinoma Progression and Sunitinib Resistance Through FOXO3a-ACSL4 Axis-regulated Ferroptosis," *International Journal of Biological Sciences* 19, no. 4 (2023): 1266–1283.

141. K. D. Tousignant, A. Rockstroh, B. L. J. Poad, et al., "Therapy-induced Lipid Uptake and Remodeling Underpin Ferroptosis Hypersensitivity in Prostate Cancer," *Cancer & Metabolism* 8 (2020): 11.

142. B. Feng, H. Y. Guo, Y. Ning, Y. Y. Zhao, X. Wang, and R. Cui, "LPCAT3 regulates the Immune Infiltration and Prognosis of ccRCC Patients by Mediating Ferroptosis and Endoplasmic Reticulum Stress," *Discover Oncology* 16, no. 1 (2025): 574.

143. Y. Qiu, X. Wang, Y. Sun, et al., "ACSL4-Mediated Membrane Phospholipid Remodeling Induces Integrin β1 Activation to Facilitate Triple-Negative Breast Cancer Metastasis," *Cancer Research* 84, no. 11 (2024): 1856–1871.

144. J. Chen, C. Ding, Y. Chen, et al., "ACSL4 reprograms Fatty Acid Metabolism in Hepatocellular Carcinoma via c-Myc/SREBP1 Pathway," *Cancer Letters* 502 (2021): 154–165.

145. A. F. Castillo, U. D. Orlando, P. M. Maloberti, et al., "New Inhibitor Targeting Acyl-CoA Synthetase 4 Reduces Breast and Prostate Tumor

Growth, Therapeutic Resistance and Steroidogenesis," *Cellular and Molecular Life Sciences* 78, no. 6 (2021): 2893–2910.

146. J. Chen, Y. Jiang, H. Shi, Y. Peng, X. Fan, and C. Li, "The Molecular Mechanisms of Copper Metabolism and Its Roles in human Diseases," *Pflugers Archiv: European Journal of Physiology* 472, no. 10 (2020): 1415–1429.

147. A. Dancis, D. G. Roman, G. J. Anderson, A. G. Hinnebusch, and R. D. Klausner, "Ferric Reductase of Saccharomyces Cerevisiae: Molecular Characterization, Role in Iron Uptake, and Transcriptional Control by Iron," *PNAS* 89, no. 9 (1992): 3869–3873.

148. J. Xie, Y. Yang, Y. Gao, and J. He, "Cuproptosis: Mechanisms and Links With Cancers," *Molecular Cancer* 22, no. 1 (2023): 46.

149. Y. Feng, Z. Yang, J. Wang, and H. Zhao, "Cuproptosis: Unveiling a New Frontier in Cancer Biology and Therapeutics," *Cell Communication and Signaling* 22, no. 1 (2024): 249.

150. B. Halliwell and J. M. Gutteridge, "Oxygen Toxicity, Oxygen Radicals, Transition Metals and Disease," *Biochemical Journal* 219, no. 1 (1984): 1–14.

151. D. Cen, D. Brayton, B. Shahandeh, and F. L. Meyskens Jr, "Farmer PJ: Disulfiram Facilitates Intracellular Cu Uptake and Induces Apoptosis in human Melanoma Cells," *Journal of Medicinal Chemistry* 47, no. 27 (2004): 6914–6920.

152. M. Yang, X. Wu, J. Hu, et al., "COMMD10 inhibits HIF1α/CP Loop to Enhance Ferroptosis and Radiosensitivity by Disrupting Cu-Fe Balance in Hepatocellular Carcinoma," *Journal of Hepatology* 76, no. 5 (2022): 1138–1150.

153. H. Wen, C. Qu, Z. Wang, et al., "Cuproptosis Enhances Docetaxel Chemosensitivity by Inhibiting Autophagy via the DLAT/mTOR Pathway in Prostate Cancer," *The FASEB Journal* 37, no. 9 (2023): e23145.

154. K. Li, L. Tan, Y. Li, et al., "Cuproptosis Identifies respiratory Subtype of Renal Cancer That Confers Favorable Prognosis," *Apoptosis* 27, no. 11-12 (2022): 1004–1014.

155. B. Cheng, C. Tang, J. Xie, et al., "Cuproptosis Illustrates Tumor Micro-environment Features and Predicts Prostate Cancer Therapeutic Sensitivity and Prognosis," *Life Sciences* 325 (2023): 121659.

156. C. Xiao, X. Wang, S. Li, et al., "A Cuproptosis-based Nanomedicine Suppresses Triple Negative Breast Cancers by Regulating Tumor Microenvironment and Eliminating Cancer Stem Cells," *Biomaterials* 313 (2025): 122763.

157. Z. Zhu, Q. Zhao, W. Song, et al., "A Novel Cuproptosis-related Molecular Pattern and Its Tumor Microenvironment Characterization in Colorectal Cancer," *Frontiers in Immunology* 13 (2022): 940774.

158. Q. Song, R. Zhou, F. Shu, and W. Fu, "Cuproptosis Scoring System to Predict the Clinical Outcome and Immune Response in Bladder Cancer," *Frontiers in Immunology* 13 (2022): 958368.

159. J. Zeng, H. Chen, X. Liu, et al., "Cuproptosis in Microsatellite Stable Colon Cancer Cells Affects the Cytotoxicity of CD8(+)T Through the WNT Signaling Pathway," *Chemico-Biological Interactions* 403 (2024): 111239.

160. Y. T. Liu, L. Chen, S. J. Li, et al., "Dysregulated Wnt/β-catenin Signaling Confers Resistance to Cuproptosis in Cancer Cells," *Cell Death and Differentiation* 31, no. 11 (2024): 1452–1466.

161. K. Wang, Y. Zhang, M. Ao, H. Luo, W. Mao, and B. Li, "Multi-omics Analysis Defines a Cuproptosis-related Prognostic Model for Ovarian Cancer: Implication of WASF2 in Cuproptosis Resistance," *Life Sciences* 332 (2023): 122081.

162. H. Nie, H. Wang, M. Zhang, et al., "Comprehensive Analysis of Cuproptosis-related Genes in Prognosis, Tumor Microenvironment Infiltration, and Immunotherapy Response in Gastric Cancer," *Journal of Cancer Research and Clinical Oncology* 149, no. 8 (2023): 5453–5468.

163. S. Song, M. Zhang, P. Xie, S. Wang, and Y. Wang, "Comprehensive Analysis of Cuproptosis-related Genes and Tumor Microenvironment Infiltration Characterization in Breast Cancer," *Frontiers in Immunology* 13 (2022): 978909.

164. W. Xie, Y. Zhang, Q. Xu, et al., "A Unique Approach: Biomimetic Graphdiyne-Based Nanoplatform to Treat Prostate Cancer by Combining Cuproptosis and Enhanced Chemodynamic Therapy," *International Journal of Nanomedicine* 19 (2024): 3957–3972.

165. X. Gao, H. Zhao, J. Liu, et al., "Enzalutamide Sensitizes Castration-Resistant Prostate Cancer to Copper-Mediated Cell Death," *Advanced Science (Weinh)* 11, no. 30 (2024): e2401396.

166. P. Koppula, L. Zhuang, and B. Gan, "Cystine Transporter SLC7A11/xCT in Cancer: Ferroptosis, Nutrient Dependency, and Cancer Therapy," *Protein Cell* 12, no. 8 (2021): 599–620.

167. Y. Yan, H. Teng, Q. Hang, et al., "SLC7A11 expression Level Dictates Differential Responses to Oxidative Stress in Cancer Cells," *Nature Communications* 14, no. 1 (2023): 3673.

168. G. Grasmann, E. Smolle, H. Olschewski, and K. Leithner, "Gluconeogenesis in Cancer Cells—Repurposing of a Starvation-induced Metabolic Pathway?," *Biochimica et Biophysica Acta: Reviews on Cancer* 1872, no. 1 (2019): 24–36.

169. T. Levy, K. Voeltzke, L. Hruby, et al., "mTORC1 regulates Cell Survival Under Glucose Starvation Through 4EBP1/2-mediated Translational Reprogramming of Fatty Acid Metabolism," *Nature Communications* 15, no. 1 (2024): 4083.

170. M. Kang, J. H. Kang, I. A. Sim, et al., "Glucose Deprivation Induces Cancer Cell Death Through Failure of ROS Regulation," *International Journal of Molecular Sciences* 24, no. 15 (2023): 11969.

171. J. Wang, J. Chen, K. Fan, et al., "Inhibition of Endoplasmic Reticulum Stress Cooperates With SLC7A11 to Promote Disulfidptosis and Suppress Tumor Growth Upon Glucose Limitation," *Advanced Science (Weinh)* 12, no. 7 (2025): e2408789.

172. A. Jiang, W. Liu, Y. Liu, et al., "DCS, a Novel Classifier System Based on Disulfidptosis Reveals Tumor Microenvironment Heterogeneity and Guides Frontline Therapy for Clear Cell Renal Carcinoma," *Journal of the National Cancer Institute* 4, no. 3 (2024): 263–279.

173. J. Xie, X. Deng, Y. Xie, et al., "Multi-omics Analysis of Disulfidptosis Regulators and Therapeutic Potential Reveals Glycogen Synthase 1 as a Disulfidptosis Triggering Target for Triple-negative Breast Cancer," *MedComm* 5, no. 3 (2024): e502.

174. D. Zhao, Y. Meng, Y. Dian, et al., "Molecular Landmarks of Tumor Disulfidptosis Across Cancer Types to Promote Disulfidptosis-target Therapy," *Redox Biology* 68 (2023): 102966.

175. C. Zhang, T. Xu, K. Ji, et al., "Development and Experimental Validation of a Machine Learning-based Disulfidptosis-related Ferroptosis Score for Hepatocellular Carcinoma," *Apoptosis* 29, no. 1-2 (2024): 103–120.

176. J. Wei, J. Wang, X. Chen, L. Zhang, and M. Peng, "Novel Application of the Ferroptosis-related Genes Risk Model Associated With Disulfidptosis in Hepatocellular Carcinoma Prognosis and Immune Infiltration," *PeerJ* 12 (2024): e16819.

177. K. Xu, D. Li, J. Qian, et al., "Single-cell Disulfidptosis Regulator Patterns Guide Intercellular Communication of Tumor Microenvironment That Contribute to Kidney Renal Clear Cell Carcinoma Progression and Immunotherapy," *Frontiers in immunology* 15 (2024): 1288240.

178. T. Jin, T. Yin, R. Xu, et al., "Exploring the Role of Disulfidptosis-related Signatures in Immune Microenvironment, Prognosis and Therapeutic Strategies of Cervical Cancer," *Translational Oncology* 44 (2024): 101938.

179. K. Newton, A. Strasser, N. Kayagaki, and V. M. Dixit, "Cell Death," *Cell* 187, no. 2 (2024): 235–256.

180. M. Zhu, D. Liu, G. Liu, M. Zhang, and F. Pan, "Caspase-Linked Programmed Cell Death in Prostate Cancer: From Apoptosis, Necroptosis, and Pyroptosis to PANoptosis," *Biomolecules* 13, no. 12 (2023): 1715.

181. Á. F. Fernández, S. Sebti, Y. Wei, et al., "Disruption of the Beclin 1-BCL2 Autophagy Regulatory Complex Promotes Longevity in Mice," *Nature* 558, no. 7708 (2018): 136–140.

182. S. Pattingre, A. Tassa, X. Qu, et al., "Bcl-2 Antiapoptotic Proteins Inhibit Beclin 1-dependent Autophagy," *Cell* 122, no. 6 (2005): 927–939.

183. R. Kang, H. J. Zeh, M. T. Lotze, and D. Tang, "The Beclin 1 Network Regulates Autophagy and Apoptosis," *Cell Death and Differentiation* 18, no. 4 (2011): 571–580.

184. W. Wang, K. Lu, X. Jiang, et al., "Ferroptosis Inducers Enhanced Cuproptosis Induced by Copper Ionophores in Primary Liver Cancer," *Journal of Experimental & Clinical Cancer Research* 42, no. 1 (2023): 142.

185. S. Zhang, Y. Wang, J. Gu, et al., "PPARγ Antagonists Exhibit Antitumor Effects by Regulating Ferroptosis and Disulfidptosis," *Biomolecules* 14, no. 5 (2024): 596.

186. C. Mao, M. Wang, L. Zhuang, and B. Gan, "Metabolic Cell Death in Cancer: Ferroptosis, Cuproptosis, Disulfidptosis, and Beyond," *Protein Cell* 15, no. 9 (2024): 642–660.

187. L. Li, T. Li, X. Qu, G. Sun, Q. Fu, and G. Han, "Stress/Cell Death Pathways, Neuroinflammation, and Neuropathic Pain," *Immunological Reviews* 321, no. 1 (2024): 33–51.

188. B. Wang, Y. Wang, J. Zhang, et al., "ROS-induced Lipid Peroxidation Modulates Cell Death Outcome: Mechanisms Behind Apoptosis, Autophagy, and Ferroptosis," *Archives of Toxicology* 97, no. 6 (2023): 1439–1451.

189. M. Kist and D. Vucic, "Cell Death Pathways: Intricate Connections and Disease Implications," *Embo Journal* 40, no. 5 (2021): e106700.

190. X. Tong, R. Tang, M. Xiao, et al., "Targeting Cell Death Pathways for Cancer Therapy: Recent Developments in Necroptosis, Pyroptosis, Ferroptosis, and Cuproptosis Research," *Journal of Hematology & Oncology* 15, no. 1 (2022): 174.

191. M. Wang, F. Yu, Y. Zhang, and P. Li, "Programmed Cell Death in Tumor Immunity: Mechanistic Insights and Clinical Implications," *Frontiers in Immunology* 14 (2024): 1309635.

192. S. Li, A. Wang, Y. Wu, et al., "Targeted Therapy for Non-small-cell Lung Cancer: New Insights Into Regulated Cell Death Combined With Immunotherapy," *Immunological Reviews* 321, no. 1 (2024): 300–334.

193. Y. Xia, J. Zhang, and G. Liu, "A Prospective Strategy Leveraging Nanomedicine for Cancer Therapy: Pouring Ferroptosis on Apoptosis," *Nano Today* 48 (2023): 101740.

194. M. Kciuk, A. Gielecińska, Ż. Kałuzińska-Kołat, E. B. Yahya, and R. Kontek, "Ferroptosis and Cuproptosis: Metal-dependent Cell Death Pathways Activated in Response to Classical Chemotherapy—Significance for Cancer Treatment?," *Biochimica et Biophysica Acta: Reviews on Cancer* 1879, no. 4 (2024): 189124.

195. N. Kyprianou, H. F. English, and J. T. Isaacs, "Programmed Cell Death During Regression of PC-82 human Prostate Cancer Following Androgen Ablation," *Cancer Research* 50, no. 12 (1990): 3748–3753.

196. C. Söhngen, D. J. Thomas, M. A. Skowron, et al., "CD24 targeting With NK-CAR Immunotherapy in Testis, Prostate, Renal and (luminal-type) Bladder Cancer and Identification of Direct CD24 Interaction Partners," *The FEBS Journal* 290, no. 20 (2023): 4864–4876.

197. X. Lu, F. Yang, D. Chen, et al., "Quercetin Reverses Docetaxel Resistance in Prostate Cancer via Androgen Receptor and PI3K/Akt Signaling Pathways," *International Journal of Biological Sciences* 16, no. 7 (2020): 1121–1134.

198. W. Wang, X. Yuan, J. Mu, et al., "Quercetin Induces MGMT(+) Glioblastoma Cells Apoptosis via Dual Inhibition of Wnt3a/β-Catenin and Akt/NF-κB Signaling Pathways," *Phytomedicine* 118 (2023): 154933.

199. A. Maugeri, A. Calderaro, G. T. Patanè, et al., "Targets Involved in the Anti-Cancer Activity of Quercetin in Breast, Colorectal and Liver Neoplasms," *International Journal of Molecular Sciences* 24, no. 3 (2023): 2952.

200. P. Maleki Dana, F. Sadoughi, Z. Asemi, and B. Yousefi, "Anti-cancer Properties of Quercetin in Osteosarcoma," *Cancer Cell International* 21, no. 1 (2021): 349.

201. C. He, Y. Zhou, Z. Li, et al., "Co-Expression of IL-7 Improves NKG2D-Based CAR T Cell Therapy on Prostate Cancer by Enhancing the Expansion and Inhibiting the Apoptosis and Exhaustion," *Cancers (Basel)* 12, no. 7 (2020): 1969.

202. D. Yang, B. Sun, H. Dai, et al., "T Cells Expressing NKG2D Chimeric Antigen Receptors Efficiently Eliminate Glioblastoma and Cancer Stem Cells," *Journal for ImmunoTherapy of Cancer* 7, no. 1 (2019): 171.

203. Y. Zhang, C. Zhang, M. He, W. Xing, R. Hou, and H. Zhang, "Co-expression of IL-21-Enhanced NKG2D CAR-NK Cell Therapy for Lung Cancer," *BMC Cancer* 24, no. 1 (2024): 119.

204. F. Almasri and R. Karshafian, "Synergistic Enhancement of Cell Death by Triple Combination Therapy of docetaxel, Ultrasound and Microbubbles, and Radiotherapy on PC3 a Prostate Cancer Cell Line," *Heliyon* 8, no. 8 (2022): e10213.

205. H. Wei, J. Huang, J. Yang, et al., "Ultrasound Exposure Improves the Targeted Therapy Effects of Galactosylated Docetaxel Nanoparticles on Hepatocellular Carcinoma Xenografts," *PLoS ONE* 8, no. 3 (2013): e58133.

206. T. Li, Z. Hu, C. Wang, et al., "PD-L1-targeted Microbubbles Loaded With Docetaxel Produce a Synergistic Effect for the Treatment of Lung Cancer Under Ultrasound Irradiation," *Biomaterials Science* 8, no. 5 (2020): 1418–1430.

207. F. Fontana, R. M. Moretti, M. Raimondi, et al., "δ-Tocotrienol Induces Apoptosis, Involving Endoplasmic Reticulum Stress and Autophagy, and Paraptosis in Prostate Cancer Cells," *Cell Proliferation* 52, no. 3 (2019): e12576.

208. F. Fontana, M. Marzagalli, M. Raimondi, V. Zuco, N. Zaffaroni, and P. Limonta, "δ-Tocotrienol Sensitizes and Re-sensitizes Ovarian Cancer Cells to Cisplatin via Induction of G1 Phase Cell Cycle Arrest and ROS/MAPK-mediated Apoptosis," *Cell Proliferation* 54, no. 11 (2021): e13111.

209. J. Shen, T. Yang, Y. Tang, et al., "δ-Tocotrienol Induces Apoptosis and Inhibits Proliferation of Nasopharyngeal Carcinoma Cells," *Food & Function* 12, no. 14 (2021): 6374–6388.

210. R. A. Francois, A. Zhang, K. Husain, et al., "Vitamin E δ-tocotrienol Sensitizes human Pancreatic Cancer Cells to TRAIL-induced Apoptosis Through Proteasome-mediated Down-regulation of c-FLIP(s)," *Cancer Cell International* 19 (2019): 189.

211. C. Ye, W. Zhao, M. Li, et al., "δ-tocotrienol Induces human Bladder Cancer Cell Growth Arrest, Apoptosis and Chemosensitization Through Inhibition of STAT3 Pathway," *PLoS ONE* 10, no. 4 (2015): e0122712.

212. H. Hu, C. Jiang, T. Schuster, G. X. Li, P. T. Daniel, and J. Lü, "Inorganic Selenium Sensitizes Prostate Cancer Cells to TRAIL-induced Apoptosis Through Superoxide/p53/Bax-mediated Activation of Mitochondrial Pathway," *Molecular Cancer Therapeutics* 5, no. 7 (2006): 1873–1882.

213. B. Toubhans, S. A. Gazze, C. Bissardon, et al., "Selenium Nanoparticles Trigger Alterations in Ovarian Cancer Cell Biomechanics," *Nanomedicine* 29 (2020): 102258.

214. M. Pei, K. Liu, X. Qu, et al., "Enzyme-catalyzed Synthesis of Selenium-doped Manganese Phosphate for Synergistic Therapy of Drug-resistant Colorectal Cancer," *Journal of Nanobiotechnology* 21, no. 1 (2023): 72.

215. S. Nie, X. He, Z. Sun, et al., "Selenium Speciation-dependent Cancer Radiosensitization by Induction of G2/M Cell Cycle Arrest and Apoptosis," *Frontiers in Bioengineering and Biotechnology* 11 (2023): 1168827.

216. Z. Lu, C. Wu, M. Zhu, et al., "Ophiopogonin D' induces RIPK1-Dependent Necroptosis in Androgen-Dependent LNCaP Prostate Cancer Cells," *International Journal of Oncology* 56, no. 2 (2020): 439–447.

217. T. Xu, W. Zhang, Y. Zhang, F. Song, and P. Huang, "Ophiopogonin D' inhibited Tumour Growth and Metastasis of Anaplastic Thyroid Cancer by Modulating JUN/RGS4 Signalling," *Journal of Cellular and Molecular Medicine* 28, no. 16 (2024): e70014.

218. H. M. Ko, W. Jee, D. Lee, H. J. Jang, and J. H. Jung, "Ophiopogonin D Increase Apoptosis by Activating p53 via Ribosomal Protein L5 and L11 and Inhibiting the Expression of c-Myc via CNOT2," *Frontiers in Pharmacology* 13 (2022): 974468.

219. C. Yang, X. Ma, Z. Wang, et al., "Curcumin Induces Apoptosis and Protective Autophagy in Castration-resistant Prostate Cancer Cells Through Iron Chelation," *Drug Design, Development and Therapy* 11 (2017): 431–439.

220. W. Wang, M. Li, L. Wang, L. Chen, and B. C. Goh, "Curcumin in Cancer Therapy: Exploring Molecular Mechanisms and Overcoming Clinical Challenges," *Cancer Letters* 570 (2023): 216332.

221. M. F. Wu, Y. H. Huang, L. Y. Chiu, S. H. Cherng, G. T. Sheu, and T. Y. Yang, "Curcumin Induces Apoptosis of Chemoresistant Lung Cancer Cells via ROS-Regulated p38 MAPK Phosphorylation," *International Journal of Molecular Sciences* 23, no. 15 (2022): 8248.

222. C. Liu, M. Rokavec, Z. Huang, and H. Hermeking, "Curcumin Activates a ROS/KEAP1/NRF2/miR-34a/b/c Cascade to Suppress Colorectal Cancer Metastasis," *Cell Death and Differentiation* 30, no. 7 (2023): 1771–1785.

223. Y. Dai, J. Desano, W. Tang, et al., "Natural Proteasome Inhibitor Celastrol Suppresses Androgen-independent Prostate Cancer Progression by Modulating Apoptotic Proteins and NF-kappaB," *PLoS ONE* 5, no. 12 (2010): e14153.

224. H. Xu, H. Zhao, C. Ding, et al., "Celastrol Suppresses Colorectal Cancer via Covalent Targeting Peroxiredoxin 1," *Signal Transduction and Targeted Therapy* 8, no. 1 (2023): 51.

225. P. Luo, Q. Zhang, S. Shen, et al., "Mechanistic Engineering of Celastrol Liposomes Induces Ferroptosis and Apoptosis by Directly Targeting VDAC2 in Hepatocellular Carcinoma," *Asian Journal of Pharmaceutical Sciences* 18, no. 6 (2023): 100874.

226. X. Chen, Y. Zhao, W. Luo, et al., "Celastrol Induces ROS-mediated Apoptosis via Directly Targeting Peroxiredoxin-2 in Gastric Cancer Cells," *Theranostics* 10, no. 22 (2020): 10290–10308.

227. X. Chen, S. Wang, L. Zhang, et al., "Celastrol Inhibited Human Esophageal Cancer by Activating DR5-Dependent Extrinsic and Noxa/Bim-Dependent Intrinsic Apoptosis," *Frontiers in Pharmacology* 13 (2022): 873166.

228. B. Ma, H. Zhang, Y. Wang, et al., "Corosolic Acid, a Natural Triterpenoid, Induces ER Stress-dependent Apoptosis in human Castration Resistant Prostate Cancer Cells via Activation of IRE-1/JNK, PERK/CHOP and TRIB3," *Journal of Experimental & Clinical Cancer Research* 37, no. 1 (2018): 210.

229. X. Luo, Z. Ye, C. Xu, et al., "Corosolic Acid Enhances Oxidative Stress-induced Apoptosis and Senescence in Pancreatic Cancer Cells by Inhibiting the JAK2/STAT3 Pathway," *Molecular Biology Reports* 51, no. 1 (2024): 176.

230. S. A. Jasim, O. Z. Khalaf, S. H. Alshahrani, et al., "An in Vitro Investigation of the Apoptosis-inducing Activity of Corosolic Acid in Breast Cancer Cells," *Iranian Journal of Basic Medical Sciences* 26, no. 4 (2023): 453–460.

231. S. D. Markowitsch, K. M. Juetter, P. Schupp, et al., "Shikonin Reduces Growth of Docetaxel-Resistant Prostate Cancer Cells Mainly Through Necroptosis," *Cancers (Basel)* 13, no. 4 (2021): 882.

232. H. Tian, H. Shang, Y. Chen, et al., "Sonosensitizer Nanoplatforms Augmented Sonodynamic Therapy-Sensitizing Shikonin-Induced Necroptosis against Hepatocellular Carcinoma," *International Journal of Nanomedicine* 18 (2023): 7079–7092.

233. X. Liu, L. Liu, X. Wang, et al., "Necroptosis Inhibits Autophagy by Regulating the Formation of RIP3/p62/Keap1 Complex in shikonin-induced ROS Dependent Cell Death of human Bladder Cancer," *Phytomedicine* 118 (2023): 154943.

234. J. Liang, X. Tian, M. Zhou, et al., "Shikonin and Chitosan-silver Nanoparticles Synergize Against Triple-negative Breast Cancer Through RIPK3-triggered Necroptotic Immunogenic Cell Death," *Biomaterials* 309 (2024): 122608.

235. L. Wang, C. Hu, Y. Zhao, and X. Hu, "Novel Smac Mimetic ASTX660 (Tolinapant) and TNF-α Synergistically Induce Necroptosis in Bladder Cancer Cells in Vitro Upon Apoptosis Inhibition," *Biochemical and Biophysical Research Communications* 602 (2022): 8–14.

236. A. Koch, B. Jeiler, J. Roedig, S. J. L. van Wijk, N. Dolgikh, and S. Fulda, "Smac Mimetics and TRAIL Cooperate to Induce MLKL-dependent Necroptosis in Burkitt's Lymphoma Cell Lines," *Neoplasia* 23, no. 5 (2021): 539–550.

237. M. Montagnani Marelli, G. Beretta, and R. M. Moretti, "Necroptosis Induced by Delta-Tocotrienol Overcomes Docetaxel Chemoresistance in Prostate Cancer Cells," *International Journal of Molecular Sciences* 24, no. 5 (2023): 4923.

238. P. Sonkusre and S. S. Cameotra, "Biogenic Selenium Nanoparticles Induce ROS-mediated Necroptosis in PC-3 Cancer Cells Through TNF Activation," *Journal of Nanobiotechnology* 15, no. 1 (2017): 43.

239. L. C. de Melo Gomes, A. B. de Oliveira Cunha, L. F. F. Peixoto, et al., "Photodynamic Therapy Reduces Cell Viability, Migration and Triggers Necroptosis in Prostate Tumor Cells," *Photochemical & Photobiological Sciences* 22, no. 6 (2023): 1341–1356.

240. Q. Zheng, T. Zou, W. Wang, et al., "Necroptosis-Mediated Synergistic Photodynamic and Glutamine-Metabolic Therapy Enabled by a Biomimetic Targeting Nanosystem for Cholangiocarcinoma," *Advanced Science (Weinh)* 11, no. 29 (2024): e2309203.

241. Á. C. de Souza, A. L. Mencalha, A. S. D. Fonseca, and F. de Paoli, "Necroptosis as a Consequence of Photodynamic Therapy in Tumor Cells," *Lasers in Medical Science* 39, no. 1 (2024): 267.

242. W. Chen, X. Wang, B. Zhao, et al., "CuS-MnS(2) Nano-flowers for Magnetic Resonance Imaging Guided Photothermal/Photodynamic Therapy of Ovarian Cancer Through Necroptosis," *Nanoscale* 11, no. 27 (2019): 12983–12989.

243. M. Montagnani Marelli, C. Macchi, M. Ruscica, P. Sartori, and R. M. Moretti, "Anticancer Activity of Delta-Tocotrienol in Human Hepatocarcinoma: Involvement of Autophagy Induction," *Cancers (Basel)* 16, no. 15 (2024): 2654.

244. S. Cocco, A. Leone, M. S. Roca, et al., "Inhibition of Autophagy by Chloroquine Prevents Resistance to PI3K/AKT Inhibitors and Potentiates Their Antitumor Effect in Combination With paclitaxel in Triple Negative Breast Cancer Models," *Journal of Translational Medicine* 20, no. 1 (2022): 290.

245. P. M. P. Ferreira, R. W. R. Sousa, J. R. O. Ferreira, G. C. G. Militão, and D. P. Bezerra, "Chloroquine and Hydroxychloroquine in Antitumor Therapies Based on Autophagy-related Mechanisms," *Pharmacological Research* 168 (2021): 105582.

246. A. Brockmueller, V. Ruiz de Porras, and M. Shakibaei, "Curcumin and Its Anti-colorectal Cancer Potential: From Mechanisms of Action to Autophagy," *Phytotherapy Research* 38, no. 7 (2024): 3525–3551.

247. X. Tang, H. Ding, M. Liang, et al., "Curcumin Induces Ferroptosis in Non-small-cell Lung Cancer via Activating Autophagy," *Thoracic Cancer* 12, no. 8 (2021): 1219–1230.

248. W. B. Wang, L. X. Feng, Q. X. Yue, et al., "Paraptosis Accompanied by Autophagy and Apoptosis Was Induced by Celastrol, a Natural Compound With Influence on Proteasome, ER Stress and Hsp90," *Journal of Cellular Physiology* 227, no. 5 (2012): 2196–2206.

249. J. Guo, Y. Mei, K. Li, X. Huang, and H. Yang, "Downregulation of miR-17-92a Cluster Promotes Autophagy Induction in Response to Celastrol Treatment in Prostate Cancer Cells," *Biochemical and Biophysical Research Communications* 478, no. 2 (2016): 804–810.

250. J. Guo, X. Huang, H. Wang, and H. Yang, "Celastrol Induces Autophagy by Targeting AR/miR-101 in Prostate Cancer Cells," *PLoS ONE* 10, no. 10 (2015): e0140745.

251. W. Zhang, Z. Wu, H. Qi, et al., "Celastrol Upregulated ATG7 Triggers Autophagy via Targeting Nur77 in Colorectal Cancer," *Phytomedicine* 104 (2022): 154280.

252. Y. Feng, B. Zhang, J. Lv, et al., "Scaffold Hopping of Celastrol Provides Derivatives Containing Pepper Ring, Pyrazine and Oxazole Substructures as Potent Autophagy Inducers Against Breast Cancer Cell Line MCF-7," *European Journal of Medicinal Chemistry* 234 (2022): 114254.

253. L. Chen, Y. Sun, M. Tang, et al., "High-dose-androgen-induced Autophagic Cell Death to Suppress the Enzalutamide-resistant Prostate Cancer Growth via Altering the circRNA-BCL2/miRNA-198/AMBRA1 Signaling," *Cell Death Discovery* 8, no. 1 (2022): 128.

254. Z. Xiang, Y. Sun, B. You, et al., "Suppressing BCL-XL Increased the High Dose Androgens Therapeutic Effect to Better Induce the Enzalutamide-resistant Prostate Cancer Autophagic Cell Death," *Cell Death & Disease* 12, no. 1 (2021): 68.

255. W. K. Martins, R. Belotto, M. N. Silva, et al., "Autophagy Regulation and Photodynamic Therapy: Insights to Improve Outcomes of Cancer Treatment," *Frontiers in Oncology* 10 (2020): 610472.

256. C. Song, W. Xu, H. Wu, et al., "Photodynamic Therapy Induces Autophagy-mediated Cell Death in human Colorectal Cancer Cells via Activation of the ROS/JNK Signaling Pathway," *Cell Death & Disease* 11, no. 10 (2020): 938.

257. A. Ghoochani, E. C. Hsu, M. Aslan, et al., "Ferroptosis Inducers Are a Novel Therapeutic Approach for Advanced Prostate Cancer," *Cancer Research* 81, no. 6 (2021): 1583–1594.

258. Y. Yang, T. Liu, C. Hu, et al., "Ferroptosis Inducer Erastin Downregulates Androgen Receptor and Its Splice Variants in Castration-Resistant Prostate Cancer," *Oncology Reports* 45, no. 4 (2021): 25.

259. W. Yangyun, S. Guowei, S. Shufen, Y. Jie, Y. Rui, and R. Yu, "Everolimus Accelerates Erastin and RSL3-induced Ferroptosis in Renal Cell Carcinoma," *Gene* 809 (2022): 145992.

260. D. Fu, C. Wang, L. Yu, and R. Yu, "Induction of Ferroptosis by ATF3 Elevation Alleviates Cisplatin Resistance in Gastric Cancer by Restraining Nrf2/Keap1/xCT Signaling," *Cellular & Molecular Biology Letters* 26, no. 1 (2021).

261. C. Desterke, Y. Xiang, R. Elhage, C. Duruel, Y. Chang, and A. Hamaï, "Ferroptosis Inducers Upregulate PD-L1 in Recurrent Triple-Negative Breast Cancer," *Cancers (Basel)* 16, no. 1 (2023): 155.

262. K. Chang, Y. Chen, X. Zhang, et al., "DPP9 Stabilizes NRF2 to Suppress Ferroptosis and Induce Sorafenib Resistance in Clear Cell Renal Cell Carcinoma," *Cancer Research* 83, no. 23 (2023): 3940–3955.

263. L. Li, J. Zeng, S. He, Y. Yang, and C. Wang, "METTL14 decreases FTH1 mRNA Stability via m6A Methylation to Promote Sorafenib-induced Ferroptosis of Cervical Cancer," *Cancer Biology & Therapy* 25, no. 1 (2024): 2349429.

264. Z. Wang, C. Zhou, Y. Zhang, et al., "From Synergy to Resistance: Navigating the Complex Relationship Between Sorafenib and Ferroptosis in Hepatocellular Carcinoma," *Biomedicine & Pharmacotherapy* 170 (2024): 116074.

265. Q. Li, K. Chen, T. Zhang, et al., "Understanding Sorafenib-induced Ferroptosis and Resistance Mechanisms: Implications for Cancer Therapy," *European Journal of Pharmacology* 955 (2023): 175913.

266. F. Maccarinelli, D. Coltrini, S. Mussi, et al., "Iron Supplementation Enhances RSL3-induced Ferroptosis to Treat Naïve and Prevent Castration-resistant Prostate Cancer," *Cell Death Discovery* 9, no. 1 (2023): 81.

267. J. Bordini, F. Morisi, A. R. Elia, et al., "Iron Induces Cell Death and Strengthens the Efficacy of Antiandrogen Therapy in Prostate Cancer Models," *Clinical Cancer Research* 26, no. 23 (2020): 6387–6398.

268. R. Rodriguez, S. L. Schreiber, and M. Conrad, "Persister Cancer Cells: Iron Addiction and Vulnerability to Ferroptosis," *Molecular Cell* 82, no. 4 (2022): 728–740.

269. X. Yao, R. Xie, Y. Cao, et al., "Simvastatin Induced Ferroptosis for Triple-negative Breast Cancer Therapy," *Journal of Nanobiotechnology* 19, no. 1 (2021): 311.

270. W. J. Tang, D. Xu, M. X. Liang, et al., "Pitavastatin Induces Autophagy-dependent Ferroptosis in MDA-MB-231 Cells via the Mevalonate Pathway," *Heliyon* 10, no. 5 (2024): e27084.

271. D. Sun, X. Cui, W. Yang, et al., "Simvastatin Inhibits PD-L1 via ILF3 to Induce Ferroptosis in Gastric Cancer Cells," *Cell Death & Disease* 16, no. 1 (2025): 208.

272. W. Mao, Y. Cai, D. Chen, et al., "Statin Shapes Inflamed Tumor Microenvironment and Enhances Immune Checkpoint Blockade in Non-small Cell Lung Cancer," *JCI Insight* 7, no. 18 (2022): e161940.

273. M. Shi, M. J. Zhang, Y. Yu, et al., "Curcumin Derivative NL01 Induces Ferroptosis in Ovarian Cancer Cells via HCAR1/MCT1 Signaling," *Cell Signalling* 109 (2023): 110791.

274. Z. Liu, H. Ma, and Z. Lai, "The Role of Ferroptosis and Cuproptosis in Curcumin Against Hepatocellular Carcinoma," *Molecules (Basel, Switzerland)* 28, no. 4 (2023): 1623.

275. X. Cao, Y. Li, Y. Wang, et al., "Curcumin Suppresses Tumorigenesis by Ferroptosis in Breast Cancer," *PLoS ONE* 17, no. 1 (2022): e0261370.

276. X. Zhou, L. Zou, W. Chen, et al., "Flubendazole, FDA-approved Anthelmintic, Elicits Valid Antitumor Effects by Targeting P53 and Promoting Ferroptosis in Castration-resistant Prostate Cancer," *Pharmacological Research* 164 (2021): 105305.

277. W. Teng, Y. Ling, N. Long, et al., "Repurposing Flubendazole for Glioblastoma Ferroptosis by Affecting xCT and TFRC Proteins," *Journal of Cellular and Molecular Medicine* 28, no. 22 (2024): e70188.

278. L. M. Khachigian, "Emerging Insights on Functions of the Anthelmintic Flubendazole as a Repurposed Anticancer Agent," *Cancer Letters* 522 (2021): 57–62.

279. L. Wu, F. Liu, L. Yin, et al., "The Establishment of Polypeptide PSMA-targeted Chimeric Antigen Receptor-engineered Natural Killer Cells for Castration-resistant Prostate Cancer and the Induction of Ferroptosis-related Cell Death," *Cancer Communications (London)* 42, no. 8 (2022): 768–783.

280. H. Wang, L. Zhang, Z. Miao, et al., "PSMA-targeted Arsenic Nanosheets: A Platform for Prostate Cancer Therapy via Ferroptosis and ATM Deficiency-triggered Chemosensitization," *Materials Horizons* 8, no. 8 (2021): 2216–2229.

281. B. Tao, R. Du, X. Zhang, et al., "Engineering CAR-NK Cell Derived Exosome Disguised Nano-bombs for Enhanced HER2 Positive Breast Cancer Brain Metastasis Therapy," *Journal of Controlled Release* 363 (2023): 692–706.

282. K. S. Kim, B. Choi, H. Choi, M. J. Ko, D. H. Kim, and D. H. Kim, "Enhanced Natural Killer Cell Anti-tumor Activity With Nanoparticles Mediated Ferroptosis and Potential Therapeutic Application in Prostate Cancer," *Journal of Nanobiotechnology* 20, no. 1 (2022): 428.

283. J. Chen, Y. Wang, L. Han, et al., "A Ferroptosis-inducing Biomimetic Nanocomposite for the Treatment of Drug-resistant Prostate Cancer," *Materials Today Bio* 17 (2022): 100484.

284. Q. T. Huang, Q. Q. Hu, Z. F. Wen, and Y. L. Li, "Iron Oxide Nanoparticles Inhibit Tumor Growth by Ferroptosis in Diffuse Large B-cell Lymphoma," *American Journal of Cancer Research* 13, no. 2 (2023): 498–508.

285. Q. Li, R. Su, X. Bao, et al., "Glycyrrhetinic Acid Nanoparticles Combined With Ferrotherapy for Improved Cancer Immunotherapy," *Acta Biomaterialia* 144 (2022): 109–120.

286. P. Zou, Z. Chen, Q. He, and Y. Zhuo, "Polyphyllin I Induces Ferroptosis in Castration-resistant Prostate Cancer Cells Through

the ERK/DNMT1/ACSL4 Axis," *Prostate* 84, no. 1 (2024): 64–73.

287. F. Zheng, Y. Wang, Q. Zhang, et al., "Polyphyllin I Suppresses the Gastric Cancer Growth by Promoting Cancer Cell Ferroptosis," *Frontiers in Pharmacology* 14 (2023): 1145407.

288. R. Yang, W. Gao, Z. Wang, et al., "Polyphyllin I Induced Ferroptosis to Suppress the Progression of Hepatocellular Carcinoma Through Activation of the Mitochondrial Dysfunction via Nrf2/HO-1/GPX4 Axis," *Phytomedicine* 122 (2024): 155135.

289. S. Liu, Y. Tao, S. Wu, et al., "Sanguinarine Chloride Induces Ferroptosis by Regulating ROS/BACH1/HMOX1 Signaling Pathway in Prostate Cancer," *Chinese Medicine* 19, no. 1 (2024): 7.

290. A. Alakkal, F. Thayyullathil, S. Pallichankandy, K. Subburayan, A. R. Cheratta, and S. Galadari, "Sanguinarine Induces H(2)O(2)-Dependent Apoptosis and Ferroptosis in Human Cervical Cancer," *Biomedicines* 10, no. 8 (2022): 1795.

291. R. Xu, J. Wu, Y. Luo, et al., "Sanguinarine Represses the Growth and Metastasis of Non-small Cell Lung Cancer by Facilitating Ferroptosis," *Current Pharmaceutical Design* 28, no. 9 (2022): 760–768.

292. W. Yang, Y. Wang, Y. Huang, et al., "4-Octyl Itaconate Inhibits Aerobic Glycolysis by Targeting GAPDH to Promote Cuproptosis in Colorectal Cancer," *Biomedicine & Pharmacotherapy* 159 (2023): 114301.

293. X. Lu, W. Deng, S. Wang, et al., "PEGylated Elesclomol@Cu(II)-based Metal–Organic Framework With Effective Nanozyme Performance and Cuproptosis Induction Efficacy for Enhanced PD-L1-based Immunotherapy," *Materials Today Bio* 29 (2024): 101317.

294. N. J. S. Bontempo, D. A. Paixão, P. Lima, et al., "Copper(II) Complex Containing 4-Fluorophenoxyacetic Acid Hydrazide and 1,10-Phenanthroline: A Prostate Cancer Cell-Selective and Low-Toxic Copper(II) Compound," *Molecules (Basel, Switzerland)* 27, no. 20 (2022): 7097.

295. W. Lei, J. Xu, Y. Ya, et al., "Disulfiram-copper Activates Chloride Currents and Induces Apoptosis With Tyrosine Kinase in Prostate Cancer Cells," *Asia-Pacific Journal of Clinical Oncology* 18, no. 2 (2022): e46–e55.

296. J. F. Machado, D. Sequeira, F. Marques, et al., "New Copper(I) Complexes Selective for Prostate Cancer Cells," *Dalton Transactions* 49, no. 35 (2020): 12273–12286.

297. Y. Liao, D. Wang, C. Gu, et al., "A Cuproptosis Nanocapsule for Cancer Radiotherapy," *Nature Nanotechnology* 19, no. 12 (2024): 1892–1902.

298. Y. Li, J. Liu, Y. Chen, R. R. Weichselbaum, and W. Lin, "Nanoparticles Synergize Ferroptosis and Cuproptosis to Potentiate Cancer Immunotherapy," *Advanced Science (Weinh)* 11, no. 23 (2024): e2310309.

299. F. Hu, J. Huang, T. Bing, et al., "Stimulus-Responsive Copper Complex Nanoparticles Induce Cuproptosis for Augmented Cancer Immunotherapy," *Advanced Science (Weinh)* 11, no. 13 (2024): e2309388.

300. B. Guo, F. Yang, L. Zhang, et al., "Cuproptosis Induced by ROS Responsive Nanoparticles With Elesclomol and Copper Combined With αPD-L1 for Enhanced Cancer Immunotherapy," *Advanced Materials* 35, no. 22 (2023): e2212267.

301. D. Zhang, Y. Chen, Y. Sun, et al., "Gambogic Acid Induces GSDME Dependent Pyroptotic Signaling Pathway via ROS/P53/Mitochondria/Caspase-3 in Ovarian Cancer Cells," *Biochemical Pharmacology* 232 (2025): 116695.

302. H. Xu, D. Zhang, R. Wei, et al., "Gambogic Acid Induces Pyroptosis of Colorectal Cancer Cells Through the GSDME-Dependent Pathway and Elicits an Antitumor Immune Response," *Cancers (Basel)* 14, no. 22 (2022): 5505.

303. B. Ouyang, C. Shan, S. Shen, et al., "AI-powered Omics-based Drug Pair Discovery for Pyroptosis Therapy Targeting Triple-negative Breast Cancer," *Nature Communications* 15, no. 1 (2024): 7560.

304. W. Xuzhang, T. Lu, W. Jin, et al., "Cisplatin-induced Pyroptosis Enhances the Efficacy of PD-L1 Inhibitor in Small-Cell Lung Cancer via GSDME/IL12/CD4Tem Axis," *International Journal of Biological Sciences* 20, no. 2 (2024): 537–553.

305. R. Y. Li, Z. Y. Zheng, Z. M. Li, et al., "Cisplatin-induced Pyroptosis Is Mediated via the CAPN1/CAPN2-BAK/BAX-caspase-9-caspase-3-GSDME Axis in Esophageal Cancer," *Chemico-Biological Interactions* 361 (2022): 109967.

306. X. Hou, J. Xu, Y. Wang, et al., "Triggering Pyroptosis by Doxorubicin-Loaded Multifunctional Nanoparticles in Combination With Decitabine for Breast Cancer Chemoimmunotherapy," *ACS Applied Materials & Interfaces* 16, no. 43 (2024): 58392–58404.

307. X. Hou, J. Xia, Y. Feng, et al., "USP47-Mediated Deubiquitination and Stabilization of TCEA3 Attenuates Pyroptosis and Apoptosis of Colorectal Cancer Cells Induced by Chemotherapeutic Doxorubicin," *Frontiers in Pharmacology* 12 (2021): 713322.

308. J. Wu, C. Ding, C. Zhang, et al., "Methionine Metabolite Spermidine Inhibits Tumor Pyroptosis by Enhancing MYO6-mediated Endocytosis," *Nature Communications* 16, no. 1 (2025): 2184.

309. R. Chen, A. Ram, J. G. Albeck, and M. Overholtzer, "Entosis Is Induced by Ultraviolet Radiation," *Iscience* 24, no. 8 (2021): 102902.

310. X. Li, J. Xu, L. Yan, et al., "Targeting Disulfidptosis With Potentially Bioactive Natural Products in Metabolic Cancer Therapy," *Metabolites* 14, no. 11 (2024): 604.

311. W. Denmeade and J. T. Isaacs, "Programmed Cell Death (Apoptosis) and Cancer Chemotherapy," *Cancer Control: Journal of the Moffitt Cancer Center* 3 (1996): 303–309.

312. S. Maniam, "Small Molecules Targeting Programmed Cell Death in Breast Cancer Cells," *International Journal of Molecular Sciences* 22, no. 18 (2021): 9722.

313. Y. Zhang, S. Sun, W. Xu, et al., "Thioredoxin Reductase 1 Inhibitor Shikonin Promotes Cell Necroptosis via Sectraps Generation and Oxygen-Coupled Redox Cycling," *Free Radical Biology and Medicine* 180 (2022): 52–62.

314. P. Chittineedi, S. L. Pandrangi, J. A. Neira Mosquera, S. N. Sánchez Llaguno, and G. J. Mohiddin, "Aqueous Nyctanthes Arbortristis and Doxorubicin Conjugated Gold Nanoparticles Synergistically Induced mTOR-dependent Autophagy-mediated Ferritinophagy in Paclitaxel-resistant Breast Cancer Stem Cells," *Frontiers in Pharmacology* 14 (2023): 1201319.

315. Y. Chen, Q. Zhou, H. Zhang, et al., "Qingdai Decoction Suppresses Prostate Cancer Growth in Lethal-stage Prostate Cancer Models," *Journal of Ethnopharmacology* 308 (2023): 116333.

316. J. Wang, J. Li, J. Liu, et al., "Interplay of Ferroptosis and Cuproptosis in Cancer: Dissecting Metal-Driven Mechanisms for Therapeutic Potentials," *Cancers (Basel)* 16, no. 3 (2024): 512.

317. L. Lin, W. He, Y. Guo, et al., "Nanomedicine-induced Programmed Cell Death in Cancer Therapy: Mechanisms and Perspectives," *Cell Death Discovery* 10 (2024): Article number: 386.

318. F. Yang, G. Zhang, N. An, et al., "Interplay of Ferroptosis, Cuproptosis, and PANoptosis in Cancer Treatment-induced Cardiotoxicity: Mechanisms and Therapeutic Implications," *Seminars in Cancer Biology* 106–107 (2024): 106–122.

319. M. Imam, J. Ji, Z. Zhang, and S. Yan, "Targeting the Initiator to Activate both Ferroptosis and Cuproptosis for Breast Cancer Treatment: Progress and Possibility for Clinical Application," *Frontiers in Pharmacology* 15 (2024): 1493188.

320. Y. Shen, D. Li, Q. Liang, M. Yang, Y. Pan, and H. Li, "Cross-talk Between Cuproptosis and Ferroptosis Regulators Defines the Tumor Microenvironment for the Prediction of Prognosis and Therapies in Lung Adenocarcinoma," *Frontiers in Immunology* 13 (2022): 1029092.

321. K. Yamashita, M. Iwatsuki, N. Yasuda-Yoshihara, et al., "Trastuzumab Upregulates Programmed Death Ligand-1 Expression

Through Interaction With NK Cells in Gastric Cancer," *British Journal of Cancer* 124, no. 3 (2021): 595–603.

322. J. Peng, J. Hamanishi, N. Matsumura, et al., "Chemotherapy Induces Programmed Cell Death-Ligand 1 Overexpression via the Nuclear Factor-κB to Foster an Immunosuppressive Tumor Microenvironment in Ovarian Cancer," *Cancer Research* 75 (2015): 5034–5045.

323. L. Yu, K. Huang, Y. Liao, L. Wang, G. Sethi, and Z. Ma, "Targeting Novel Regulated Cell Death: Ferroptosis, Pyroptosis and Necroptosis in Anti-PD-1/PD-L1 Cancer Immunotherapy," *Cell Proliferation* 57, no. 8 (2024): e13644.

324. G. Xie, H. Dong, Y. Liang, J. D. Ham, R. Rizwan, and J. Chen, "CAR-NK Cells: A Promising Cellular Immunotherapy for Cancer," *EBioMedicine* 59 (2020): 102975.

325. Z. Pang, Z. Wang, F. Li, C. Feng, and X. Mu, "Current Progress of CAR-NK Therapy in Cancer Treatment," *Cancers (Basel)* 14, no. 17 (2022).

326. W. Li, X. Wang, X. Zhang, A. U. R. Aziz, and D. Wang, "CAR-NK Cell Therapy: A Transformative Approach to Overcoming Oncological Challenges," *Biomolecules* 14, no. 8 (2024).

327. A. B. Dezfouli, M. Yazdi, A. G. Pockley, et al., "NK Cells Armed With Chimeric Antigen Receptors (CAR): Roadblocks to Successful Development," *Cells* 10, no. 12 (2021).

328. Z. Mao, Y. Hu, and Y. Zhao, "The Mutual Regulatory Role of Ferroptosis and Immunotherapy in Anti-tumor Therapy," *Apoptosis* 29 (2024): 1291–1308.

329. S. Li, J. Shapiro, and H. Shah, "Abstract 5350: Decr2 Regulates Tumor Cell Ferroptosis and Immunotherapy Efficacy," *Cancer Research* 84, no. 6_Supplement (2024): 5350.

330. L. Xie, J. Li, G. Wang, et al., "Phototheranostic Metal-Phenolic Networks With Antiexosomal PD-L1 Enhanced Ferroptosis for Synergistic Immunotherapy," *Journal of the American Chemical Society* 144, no. 2 (2022): 787–797.

331. P. Liu, X. Shi, Y.-Y. Peng, J. Hu, J. Ding, and W. Zhou, "Anti-PD-L1 DNAzyme Loaded Photothermal Mn2+/Fe3+ Hybrid Metal-Phenolic Networks for Cyclically Amplified Tumor Ferroptosis-Immunotherapy," *Advanced Healthcare Materials* 11, no. 8 (2021): e2102315.

332. S. Jeong, B. Jung, D. Lee, et al., "Enhanced Immunogenic Cell Death by Apoptosis/Ferroptosis Hybrid Pathway Potentiates PD-L1 Blockade Cancer Immunotherapy," *ACS Biomaterials Science & Engineering* 8, no. 12 (2022): 5188–5198.

333. C. Yan, Y. Liu, G. Zhao, et al., "Inhalable Metal–organic Framework-mediated Cuproptosis Combined With PD-L1 Checkpoint Blockade for Lung Metastasis Synergistic Immunotherapy," *Acta Pharmaceutica Sinica B* 14 (2024): 2281–2297.

334. X. Lu, W. Deng, and S. Wang, "PEGylated Elesclomol@Cu(II)-based Metal–Organic Framework With Effective Nanozyme Performance and Cuproptosis Induction Efficacy for Enhanced PD-L1-based Immunotherapy," *Materials Today Bio* 29 (2024): 101317.

335. C. He, N. Zhu, Y. Chen, et al., "Reshaping Immunosuppressive Tumor Microenvironment Using Ferroptosis/Cuproptosis Nanosensitizers for Enhanced Radioimmunotherapy," *Advanced Functional Materials* 34, no. 51 (2024): 2409966.

336. F. Wang, L. Wu, L. Yin, H. Shi, Y. Gu, and N. Xing, "Combined Treatment With Anti-PSMA CAR NK-92 Cell and Anti-PD-L1 Monoclonal Antibody Enhances the Antitumour Efficacy Against Castration-resistant Prostate Cancer," *Clinical and Translational Medicine* 12, no. 6 (2022): e901.

337. H. Wu, "Multiple Cancer Treatment Advances With CAR-NK," *Highlights in Science, Engineering and Technology*, no. 36 (2023): 930–938.

338. M. Gang, N. D. Marin, P. Wong, et al., "CAR-Modified Memory-Like NK Cells Exhibit Potent Responses to NK-Resistant Lymphomas," *Blood* 136, no. 20 (2020): 2308–2318.

339. C. Belka, V. Heinrich, P. Marini, et al., "Ionizing Radiation and the Activation of Caspase-8 in Highly Apoptosis-sensitive Lymphoma Cells," *International Journal of Radiation Biology* 75, no. 10 (1999): 1257–1264.

340. H. Li, T. Yang, J. Zhang, et al., "Pyroptotic Cell Death: An Emerging Therapeutic Opportunity for Radiotherapy," *Cell Death Discovery* 10 (2024): Article number: 32.

341. E. Mališić, N. Petrović, M. Brengues, et al., "Association of Polymorphisms in TGFB1, XRCC1, XRCC3 Genes and CD8 T-lymphocyte Apoptosis With Adverse Effect of Radiotherapy for Prostate Cancer," *Scientific Reports* 12, no. 1 (2022): 21306.

342. M. I. Koukourakis, D. Kalamida, A. Mitrakas, et al., "Intensified Autophagy Compromises the Efficacy of Radiotherapy Against Prostate Cancer," *Biochemical and Biophysical Research Communications* 461, no. 2 (2015): 268–274.

343. A. Mishra, B. Salehi, M. Sharifi-Rad, et al., "Programmed Cell Death, From a Cancer Perspective: An Overview," *Molecular Diagnosis & Therapy* 22 (2018): 281–295.

344. D. Feng, L. Li, D. Li, et al., "Prolyl 4-hydroxylase Subunit Beta (P4HB) Could Serve as a Prognostic and Radiosensitivity Biomarker for Prostate Cancer Patients," *European Journal of Medical Research* 28, no. 1 (2023): 245.

345. X. Shi, D. Feng, P. Han, and W. Wei, "Ferroptosis-related ACSL3 and ACTC1 Predict Metastasis-free Survival for Prostate Cancer Patients Undergoing Radical Radiotherapy," *Asian Journal of Surgery* 46, no. 6 (2023): 2489–2490.

346. N. Liu and M. Chen, "Crosstalk Between Ferroptosis and Cuproptosis: From Mechanism to Potential Clinical Application," *Biomedicine & Pharmacotherapy* 171 (2024): 116115.

347. G. Liu, X. Lv, Y. Ding, and Y. Guo, "Precise Medicine of Programmed Cell Death-1/Programmed Cell Death 1 Ligand 1 Inhibitor Immunotherapy Combined Radiotherapy for Inoperable Advanced Lung Cancer," *Medicine* 100, no. 24 (2021): e26367.

348. Y. Huang, H. Li, L. Peng, et al., "Programmed Cell Death 1 Inhibitors With or Without Concurrent Brain Radiotherapy for Lung Cancer Patients With Brain Metastases," *Annals of Palliative Medicine* 10 (2021): 9974–9983.

349. R. Rosell, A. Jain, J. Codony-Servat, E. Jantus-Lewintre, B. Morrison, and J. B. Ginesta, "González-Cao M: Biological Insights in Non-small Cell Lung Cancer," *Cancer Biology & Medicine* 20, no. 7 (2023): 500–518.

350. P. Seneci, "Small Molecules as Pro-apoptotic Anticancer Agents," *Pharmaceutical Patent Analyst* 1, no. 4 (2012): 483–505.

351. S. Jin, H. Wang, Z. Zhang, and M. Yan, "Targeting Ferroptosis: Small-Molecule Inducers as Novel Anticancer Agents," *Anti-Cancer Agents in Medicinal Chemistry* 25, no. 8 (2025): 517–532.

352. B. Sun, L. Zhang, B. Wu, and X. Luo, "A Morpholine Derivative N-(4-morpholinomethylene)ethanesulfonamide Induces Ferroptosis in Tumor Cells by Targeting NRF2," *Biological & Pharmaceutical Bulletin* 47, no. 2 (2024): 417–426.

353. X. Ning, H. Qi, Y. Yuan, et al., "Identification of a New Small Molecule That Initiates Ferroptosis in Cancer Cells by Inhibiting the System Xc- to Deplete GSH," *European Journal of Pharmacology* 934 (2022): 175304.

354. W. Taylor, S. R. Fedorka, I. Gad, et al., "Small-Molecule Ferroptotic Agents With Potential to Selectively Target Cancer Stem Cells," *Scientific Reports* 9 (2019): 5926.

355. Y. Vinik, A. Maimon, V. Dubey, et al., "Programming a Ferroptosis-to-Apoptosis Transition Landscape Revealed Ferroptosis Biomarkers and Repressors for Cancer Therapy," *Advanced Science* 11, no. 17 (2024): e2307263.

356. X. Liu, L. Zhuang, and B. Gan, "Disulfidptosis: Disulfide Stress-Induced Cell Death," *Trends in Cell Biology* 34, no. 4 (2024): 327–337.

357. D. Liang, Y. Feng, F. Zandkarimi, et al., "Ferroptosis Surveillance Independent of GPX4 and Differentially Regulated by Sex Hormones," *Cell* 186, no. 13 (2023): 2748–2764.e2722.

358. R. R. Chhipa, Y. Wu, and C. Ip, "AMPK-mediated Autophagy Is a Survival Mechanism in Androgen-dependent Prostate Cancer Cells Subjected to Androgen Deprivation and Hypoxia," *Cell Signalling* 23, no. 9 (2011): 1466–1472.

359. H. L. Bennett, J. Stockley, J. T. Fleming, et al., "Does Androgen-ablation Therapy (AAT) Associated Autophagy Have a Pro-survival Effect in LNCaP human Prostate Cancer Cells?," *Bju International* 111, no. 4 (2013): 672–682.

360. Y. Feng, H. Cao, Z. Song, L. Chen, D. Wang, and R. Gao, "Qi Ling Decoction Enhances Abiraterone Treatment via Suppression of Autophagy in Castration Resistant Prostate Cancer," *Aging (Albany NY)* 14, no. 24 (2022): 9942–9950.

361. T. Ueno, N. Masuda, S. Kamigaki, et al., "Differential Involvement of Autophagy and Apoptosis in Response to Chemoendocrine and Endocrine Therapy in Breast Cancer: Jbcrg-07tr," *International Journal of Molecular Science* 20, no. 4 (2019).

362. H.-M. Wu, J.-C. Cheng, H. S. Wang, H. Y. Huang, C. D. MacCalman, and P. C. Leung, "Gonadotropin-Releasing Hormone Type II Induces Apoptosis of Human Endometrial Cancer Cells," *Cancer Research* 69, no. 10 (2009): 4202–4208.

363. H. M. Wu, A. V. Schally, J. C. Cheng, M. Zarandi, J. Varga, and P. C. Leung, "Growth Hormone-Releasing Hormone Antagonist Induces Apoptosis of Human Endometrial Cancer Cells Through Pkcδ-Mediated Activation of P53/P21," *Cancer Letters* 298, no. 1 (2010): 16–25.

364. H. Wang, Y. Wu, S. Chen, M. Hou, Y. Yang, and M. Xie, "Construction and Validation of a Ferroptosis-Related Prognostic Model for Endometrial Cancer," *Frontiers in Genetics* 12 (2021): 729046.

365. Y. Qian, H. Chen, P. Miao, et al., "Integrated Identification and Immunotherapy Response Analysis of the Prognostic Signature Associated With M6a, Cuproptosis-Related, Ferroptosis-Related Lncrna in Endometrial Cancer," *Cancer Reports (Hoboken)* 7, no. 9 (2024): e70009.

366. A. Hagege, D. Ambrosetti, J. Boyer, et al., "The Polo-Like Kinase 1 Inhibitor onvansertib Represents a Relevant Treatment for Head and Neck Squamous Cell Carcinoma Resistant to Cisplatin and Radiotherapy," *Theranostics* 11, no. 19 (2021): 9571–9586.

367. G. M. Springett, K. Husain, A. Neuger, et al., "A Phase I Safety, Pharmacokinetic, and Pharmacodynamic Presurgical Trial of Vitamin E δ-tocotrienol in Patients With Pancreatic Ductal Neoplasia," *EBioMedicine* 2, no. 12 (2015): 1987–1995.

368. A. Colville, J. Y. Liu, C. Rodriguez-Mateo, et al., "Death-seq Identifies Regulators of Cell Death and Senolytic Therapies," *Cell Metabolism* 35, no. 10 (2023): 1814–1829.e1816.

369. L. Hao, A. Zhang, D. Lv, L. Cong, Z. Sun, and L. Liu, "EGCG Activates Keap1/P62/Nrf2 Pathway, Inhibits Iron Deposition and Apoptosis in Rats With Cerebral Hemorrhage," *Scientific Reports* 14, no. 1 (2024): 31474.

370. R. Yang, D. Yu, J. Ren, et al., "CD44 Deficiency Induces Combinatory NRF2 Inhibition and Endoplasmic Reticulum Stress-Associated Dyserythropoiesis," *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology* 39, no. 11 (2025): e70695.