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# Targeting regulated cell death pathways in cancers for effective treatment: a comprehensive review

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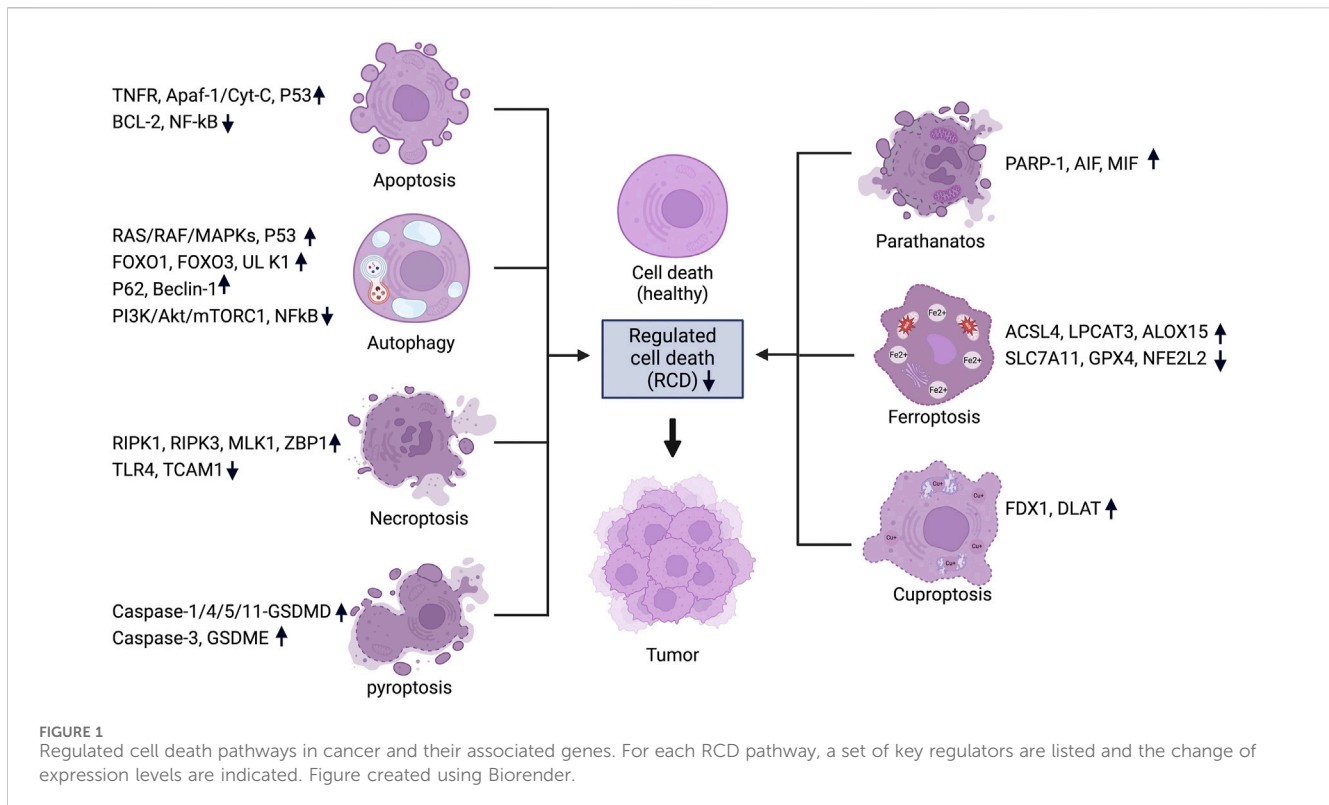
Cancer is a complex disease characterized by specific “mission-critical” events that drive the uncontrolled growth and spread of tumor cells and their offspring. These events are essential for the advancement of the disease. One of the main contributors to these events is dysregulation of cell death pathways—such as apoptosis, necroptosis, ferroptosis, autophagy, pyroptosis, cuproptosis, parthanatos and—allows cancer cells to avoid programmed cell death and continue proliferating unabated. The different cell death pathways in cancers provide useful targets for cancer treatment. This review examines recent progresses in the preclinical and clinical development of targeting dysregulated cell death pathways for cancer treatment. To develop effective cancer therapies, it is essential to identify and target these mission-critical events that prevent tumor cells from timely death. By precisely targeting these crucial events, researchers can develop therapies with maximum impact and minimal side effects. A comprehensive understanding of the molecular and cellular mechanisms underlying these regulated cell death pathways will further the development of highly effective and personalized cancer treatments.

## KEYWORDS

regulated cell death pathway, cancer therapy, apoptosis, autophagy, necroptosis, ferroptosis, pyroptosis, cuproptosis

## 1 Introduction

Cancer, an intricate disease characterized by uncontrolled cell proliferation and evasion of regulated cell death mechanisms, is a significant global health concern (Brown et al., 2023; Bhat et al., 2024). Among the several cellular mechanisms disrupted in cancer, the regulation of cell death pathways is crucial (Peng et al., 2022; Tong et al., 2022; Gong et al., 2023; Hadian and Stockwell, 2023). Programmed cell death (PCD), also known as regulated cell death (RCD), is a genetically controlled process in which cells die in an orderly manner (Koren and Fuchs, 2021; Gong et al., 2023). RCD encompasses several mechanisms, including apoptosis, necroptosis, autophagy and the newly identified pathways of pyroptosis, ferroptosis, cuproptosis, and parthanatos (Galluzzi et al., 2018) (Figure 1). Each of these mechanisms is crucial for maintaining cellular balance and responding to cellular stress (Tang et al., 2019; Lamichhane and Samir, 2023). When mammalian cells experience irreversible disruptions in their internal or external milieu, they can initiate several signal transduction cascades that ultimately result in cell death (Kayagaki et al., 2024; Newton et al., 2024). In cancer, the disruption of these pathways not only enables the



initiation and progression of tumors but also significantly affects treatment resistance and patient outcomes (Table 1) (Gong et al., 2023). Each of these RCD patterns is triggered and propagated through molecular pathways that exhibit significant connectivity (Tang et al., 2019) (Figure 2). Each variant of RCD exhibits a diverse array of morphological characteristics, ranging from complete to partial programmed cell death, which elicit unique immunomodulatory properties, including anti-inflammatory effects, promotion of immune tolerance, enhancement of inflammation, and immunogenicity. Apoptosis, marked by regulated cell shrinkage and membrane blebbing, typically leads to anti-inflammatory outcomes since apoptotic cells are phagocytosed without provoking immune activation (Elmore, 2007). Autophagy is a process of cellular degradation that generally promotes cell survival; however, under prolonged stress, it can result in cell death. Autophagy can either suppress or promote inflammation based on the context, as it regulates the immune response by degrading immune modulators or releasing signals that activate immune cells (Liu et al., 2023). Necroptosis, characterized by membrane rupture and the release of cellular contents, triggers inflammation by activating immune cells via damage-associated molecular patterns (DAMPs) (Kaczmarek et al., 2013). In a similar manner, pyroptosis, characterized by pore formation and cell lysis, enhances inflammation through the release of pro-inflammatory cytokines such as IL-1 $\beta$  (Liu Y. et al., 2024). Cuproptosis, a form of cell death that relies on copper, inflicts damage on the mitochondria and has the potential to trigger immune responses, although its specific immunomodulatory characteristics are still under investigation (Springer et al., 2024). Ferroptosis, initiated by iron-dependent lipid peroxidation, has the potential to promote inflammation via the release of DAMPs, which

in turn can affect immune responses (Qi and Peng, 2023). Parthanatos, resulting from excessive PARP activation that leads to significant DNA damage, can trigger inflammation while potentially fostering immune tolerance in chronic conditions (Huang et al., 2022). In summary, these RCD pathways influence immune dynamics by either inhibiting or facilitating immune activation, thereby affecting cancer progression and treatment results. (Galluzzi et al., 2018; Liao M. et al., 2022).

Targeting various RCD pathways to treat cancer has been under intensive investigation for several decades (Peng et al., 2022). Research in the last decade has revealed novel RCD pathways and with these discoveries, progress has been made in clinical application to target these newly identified pathways for cancer treatment (Man et al., 2017; Seehawer et al., 2018; Zhou et al., 2021; Wang Y. et al., 2022; Zhang C. et al., 2022). Furthermore, therapeutic approaches that target these RCD pathways have been used in combination with immunotherapeutic agents to further enhance their efficacies (Tong et al., 2022). Such combined approaches have the potential to significantly improve patient outcomes. Despite notable advancements, major challenges such as treatment resistance exist. This review summarizes recent advancement in preclinical and clinical development to target RCD pathways in cancer from a therapeutic standpoint, exploring how alterations in these mechanisms contribute to cancer development and impact the efficacy of current treatment methods.

## 1.1 Dysregulated apoptosis in cancer and targeting strategies for therapy

Apoptosis is a vital intracellular mechanism that maintains tissue homeostasis in an organism by regulating cell populations

TABLE 1 Role of RCD pathways in cancer.

Dysregulated pathway	Cancer type	Dysregulated gene/mechanism	Mechanism of chemoresistance	References
Apoptosis	Pancreatic cancer, ovarian cancer, lymphoma, multiple myeloma, lung adenocarcinoma, prostate cancer	Overexpression of anti-apoptotic BCL2 family proteins	Resistance to apoptosis through BCL2	Lowe and Lin (2000), Walensky et al. (2004), Del Gaizo Moore et al. (2007), Mohammad et al. (2015)
Apoptosis	Non-Small Cell Lung Cancer	Overexpression of Bcl-2 and downregulation of Bax	Inhibits chemotherapy-induced apoptosis, leading to cisplatin resistance	Alam et al. (2022)
Apoptosis	Chronic Lymphocytic Leukemia	Overexpression of Bcl-2 family proteins	Inhibition of apoptosis leading to fludarabine resistance	Tzifi et al. (2012)
Apoptosis	Prostate Cancer	P53 mutation	Impaired apoptotic response causing docetaxel resistance	Gan et al. (2011)
Apoptosis	Colon Cancer	CSC overexpress death receptors (DR4, DR5)	Increased resistance to apoptosis, reduced sensitivity to TRAIL therapy	Sussman et al. (2007)
Apoptosis	Breast cancer	Chemoresistant CSC-like population with elevated FAS, DR5	Resistance to apoptosis, potential therapeutic targeting with FAS ligand	Wang and Scadden (2015)
Apoptosis	solid tumors and myeloid leukemias	Upregulation of XIAP, inhibition of CASP3/7	Resistance to apoptosis in the presence of apoptotic signals	Tamm et al. (2000), Fulda and Vucic (2012), Monian and Jiang (2012), Amaravadi et al. (2015), Yang et al. (2019)
Apoptosis	hematological malignancies, melanoma, testicular germ cell tumor, hepatocellular carcinoma, breast cancer, urothelial carcinoma, ovarian cancer	Amplification/overexpression of MCL1	Suppresses mitochondrial pro-apoptotic proteins	Wertz et al. (2011), Carneiro and El-Deiry (2020), Satta and Grant (2020), Wei et al. (2020), Widden and Placzek (2021), Li et al. (2024a)
Autophagy	Breast cancer	Sustained JNK activation, Beclin1 release, p62 accumulation	Autophagy linked to cellular senescence,	Choi et al. (2020)
Autophagy	Glioblastoma	CDK4 downregulation	Impairs autophagy	Giordano et al. (2023)
Autophagy	Ovarian Cancer	Downregulation of ATG14, FOXP1	Enhances sensitivity to cisplatin, autophagy promotes chemoresistance	Hu et al. (2020)
Autophagy	Hepatocellular carcinoma	P62 accumulation	preventing oncogene-induced senescence and death of cancer-initiating cells	Taniguchi et al. (2016)
Autophagy	Lung cancer, Liver cancer, myeloma	Decreased Beclin-1 and P62 accumulation	P62 accumulation leads to altered NF- $\kappa$ B and inflammation signaling	Park et al. (2013), Tucci et al. (2014)
Autophagy	Non-Small Cell Lung Cancer	ATG3 upregulation	ATG3 upregulation weakened miR-1-induced apoptosis in cisplatin-resistant non-small cell lung cancer (NSCLC) cells	Hua et al. (2018)
Necroptosis	Breast Cancer, Colorectal cancer, Ovarian cancer, Acute myeloid leukemia (AML), Melanoma	downregulation of RIPK3 expression	Reduced necroptosis leads to poor survival and chemoresistance	Feng et al. (2015), Koo et al. (2015), Wang et al. (2020), Morgan and Kim (2022)
Necroptosis	AML (with Sorafenib use)	Sorafenib inhibits MLKL phosphorylation in SMAC mimetic-induced necroptosis	Reduces sensitivity to necroptosis, maintaining chemoresistance	Feldmann et al. (2017)
Necroptosis	Colorectal cancer	Metabolic reprogramming and hypoxia reduce RIPK1/RIPK3 expression	Anaerobic glycolysis and pyruvate scavenging of ROS confer necroptosis resistance	Huang and Yu (2015)

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TABLE 1 (Continued) Role of RCD pathways in cancer.

Dysregulated pathway	Cancer type	Dysregulated gene/mechanism	Mechanism of chemoresistance	References
Pyroptosis	Melanoma, HER2+ Breast Cancer	Low GSDME/GSDMB expression	Impairs pyroptosis, resulting in decreased immune cell infiltration	Lage et al. (2001), Hergueta-Redondo et al. (2016), Molina-Crespo et al. (2019)
Ferroptosis	Lung Cancer	Overexpression of SLC7A11 activated by SOX2	Increases resistance to ferroptosis through cystine transport	Wang et al. (2021c)
Ferroptosis	Colorectal Cancer	p53 boosts antioxidant defenses	Limits ferroptosis, contributing to therapy resistance	Xie et al. (2017)
Ferroptosis	Breast Cancer	GPX4 overexpression	Prevents lipid peroxidation, leading to resistance to chemotherapy	Li et al. (2021)
Ferroptosis	Ovarian Cancer	Dysregulation of SLC7A11/High GPX4 activity	Inhibits ferroptosis, aiding in chemoresistance	Qin et al. (2023), Fantone et al. (2024)
Ferroptosis	Pancreatic Cancer	High GPX4 activity	Protects against ferroptosis	Ye et al. (2021b)
Ferroptosis	Prostate Cancer, Melanoma, Sarcoma	Altered iron metabolism and Fenton reaction	Promotes resistance to oxidative stress, preventing ferroptosis	Piccolo et al. (2024)
Ferroptosis	Glioblastoma	Upregulation of antioxidant pathways independent of GPX4	Blocks ferroptosis, supporting survival against oxidative stress	Hangauer et al. (2017)
Cuproptosis	Prostate Cancer Breast Cancer	Abnormal copper regulation and elevated serum copper levels	Copper promotes metastasis and resistance through metabolic activation	Safi et al. (2014), Blockhuys et al. (2017), Blockhuys and Wittung-Stafshede (2017)
Cuproptosis	Lung Adenocarcinoma, Glioma	High-risk group associated with immune escape through cuproptosis-related lncRNAs	Reduces response to immunotherapy	Ma et al. (2022), Wang et al. (2022b), Wang et al. (2022c)
Parthanatos	Breast Cancer, Ovarian cancer, oral cancer	Overexpression of PARP-1	Enhanced chemoresistance	Harraz et al. (2008), Fong et al. (2009), Galia et al. (2012), Dorsam et al. (2018), Pazzaglia and Pioli (2019), Wang et al. (2021a)

(Elmore, 2007; Akhtar and Bokhari, 2024) (Figure 1). However, in cancer, cells lose their capacity to undergo apoptosis-induced death, which results in unchecked cell proliferation (Morana et al., 2022). Therefore, targeting the regulation of the apoptosis signaling pathway can be one of the crucial methods to improve cancer treatment (Pfeffer and Singh, 2018). Apoptosis is characterized by cell shrinkage, chromatin condensation, membrane blebbing, DNA breakage, and apoptotic body formation (Elmore, 2007). It involves two primary pathways: the extrinsic pathway, triggered by death receptors, and the intrinsic pathway, regulated by mitochondria (Zhang et al., 2005; Jan and Chaudhry, 2019) (Figure 2). The extrinsic pathways are controlled by transmembrane death receptors belonging to the CD95 (Apo-1 or Fas)/TRAIL/tumor-necrosis factor (TNF) receptor 1 family. When death ligands such as TNF $\alpha$  (tumor necrosis factor- $\alpha$ ), Fas ligand (FasL), or TRAIL bind to their corresponding cell surface receptors—TNFR1, Fas, and death receptors 4 and 5 (DR4/5)—it triggers a signaling cascade. This ligand-receptor interaction leads to the recruitment and activation of caspase-8, an initiator caspase, which in turn activates downstream effector caspases (Annibaldi and Walczak, 2020). The mitochondrion is involved in the other primary route that is responsible for death signaling. It performs the function of an integrating sensor of numerous death insults by releasing cytochrome c into the cytosol, where it then activates caspase. It is believed that the mitochondrial route is the primary

target of survival signaling pathways (Elmore, 2007). The Bcl-2 family controls the mitochondrial (intrinsic) pathway, which is triggered by damage of the mitochondria and the subsequent release of cytochrome c. This route is initiated by cytotoxic agents and UV radiation. Cytochrome c, Apaf-1, d-ATP/ATP, and procaspase-9 interact to form an apoptosome, which then triggers the caspase cascade (Wang and Youle, 2009). Additionally, a third pathway related to endoplasmic reticulum (ER) stress has also been described (Iurlaro and Munoz-Pinedo, 2016). Stress causes mutant proteins to accumulate in the endoplasmic reticulum, disrupting the balance between protein folding and protein requirement. This event triggers the unfolded protein response (UPR), which identifies and modulates ER stress (Schroder and Kaufman, 2005; Gardner et al., 2013). Key sensors in the UPR—ATF6 (activating transcription factor 6), IRE1 $\alpha$  (inositol-requiring enzyme 1 alpha), and PERK (protein kinase R-like ER kinase)—are activated when misfolded protein concentrations exceed a certain threshold. If the stress is too severe or prolonged, the UPR can shift from a protective role to triggering apoptosis, in order to eliminate the affected cell and prevent damage (Spencer and Finnie, 2020). Despite having distinct mechanisms of initiation, these intrinsic, extrinsic and stress-induced pathways all lead to activation of a series of proteolytic enzymes that are members of the caspase family (Elmore, 2007; McIlwain et al., 2015) (Figure 2). The caspases, which are cascades of cysteine aspartyl

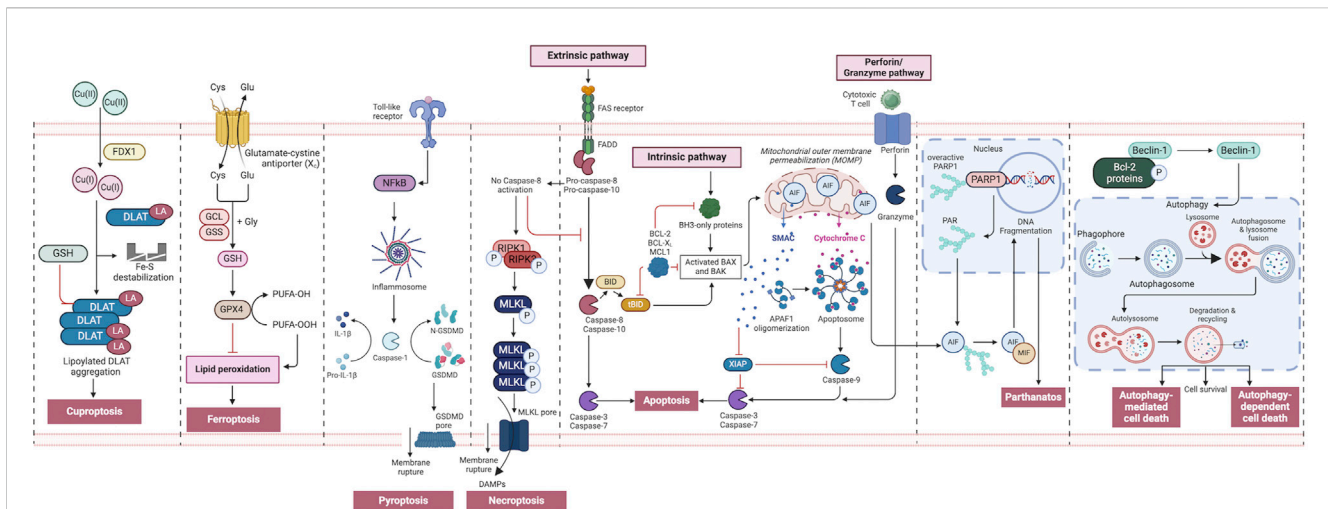


FIGURE 2

An overview of regulated cell death processes. A summary of the RCD pathways involved in cancer pathogenesis. Intrinsic apoptosis: Following an inherent fatal signal, BH3-only proteins activate BAX and BAK either directly or indirectly by binding to and blocking BCL-2 proteins. The mitochondrial outer membrane is then permeabilized (MOMP), releasing cytochrome C (Cyt C) and SMAC, the latter of which can suppress apoptosis. The apoptosome is subsequently produced, which activates caspase-9, followed by caspases 3 and 7, and initiates apoptosis. Extrinsic apoptosis: When death receptors (TNFR1, FAS, or TRAIL-R) receive an extrinsic fatal signal, they join with pro-caspase-8 and -10 to create complex I. Complex IIa is then generated, resulting in caspase-8 and -10 activation. Apoptosis is then initiated either directly by cleaving caspases-3 and -7, or indirectly by cleaving BID into tBID and activating BAX and BAK. Caspase pathway: Cytotoxic T-cells are the main controllers for the granzyme pathway, which results in caspase-10 activation that in turn activates caspase-3. Granzyme B can activate caspases in the targeted cell. Necroptosis occurs when an extrinsic fatal signal is received but caspase-8 is not activated. Complex IIb (also known as the necrosome) is generated. This causes RIPK1 and 3 to phosphorylate and activate mixed lineage kinase domain-like pseudokinase (MLKL). MLKL then forms a complex, causing the release of cytokines, chemokines, and damage-associated molecular patterns (DAMPs). Finally, this causes inflammation and necroptosis of the cell. Pyroptosis occurs when toll-like receptors (e.g., TLR4) detect an external fatal signal. Nuclear factor kappa B (NF- $\kappa$ B) signaling is initiated. This causes inflammasome development and subsequent caspase-1 activation. Then, pro-IL-1 $\beta$  is converted to active IL-1 $\beta$ , and gasdermin D (GSDMD) is broken down into N-GSDMD fragments resulting in inflammation and pyroptosis of the cell. Parthanatos occurs when an inherent fatal signal arises (for example, high reactive oxygen species accumulation), poly [ADP-ribose] polymerase 1 (PARP-1) is activated. Overactivation of PARP-1 can result in the accumulation of PAR polymer and the translocation of apoptosis inhibitory factor (AIF) from the mitochondria. AIF forms a compound with macrophage migration inhibitory factor (MIF) and re-enters the nucleus. Ultimately, this leads to cell parthanatos and DNA fragmentation. Autophagic Cell Death: Beclin-1 generally forms a complex with Bcl-2 proteins. After they have been phosphorylated and inactivated, free Beclin-1 can start autophagy. Ferroptosis occurs exclusively when there is an imbalance in the regulatory system, leading to the accumulation of lipid peroxide to a lethal threshold. Transferrin (TF) binds to extracellular Fe<sup>3+</sup> and facilitates its transport into cells via transferrin receptor 1 (TfR1), where it is then converted to Fe<sup>2+</sup>. Later, intracellular divalent metal transporter 1 (DMT1) and zinc transporter 8/14 (ZIP8/14) store the Fe<sup>2+</sup> in the intracellular labile iron pool (LIP). Fe<sup>2+</sup> transfers electrons through the Fenton reaction with peroxide, resulting in the production of oxidizing free radicals. Following an excessive accumulation of iron within cells, numerous free radicals interact with polyunsaturated fatty acids (PUFA) found in the phospholipids of cell membranes resulting in the formation of lipid peroxides, which ultimately lead to cell death. The intracellular antioxidant stress system depends on GPX4 to eliminate surplus lipid peroxides. The Cystine/glutamate antiporter (system xc<sup>-</sup>) facilitates the movement of glutamate from within cells to the outside, while simultaneously transporting cystine from the outside into cells. Cuproptosis: FDX1 plays a crucial role as a copper ion carrier in the induction of cell death and is involved in the regulation of protein lipoylation. Elevated copper levels foster the accumulation and functional impairment of lipoylated proteins, leading to instability of iron-sulfur cluster proteins, protein toxicity stress, and ultimately cell death. In addition, excessive copper binds to lipoylated DLAT, triggering abnormal oligomerization of DLAT and the formation of DLAT foci. This process contributes to cellular protein toxicity stress, further exacerbating cell death. Figure created using Biorender.

proteases are produced as dormant zymogens, which are then activated by proteolytic cleavage. This is normally accomplished by the action of upstream apical caspases (McIlwain et al., 2015). Apart from these intrinsic, extrinsic and stress-induced processes, there exists an additional pathway that entails T cell mediated cytotoxicity and perforin/granzyme-dependent cell death. The cell death inducing enzymes in this pathway are granzyme B and granzyme A proteases (Trapani and Smyth, 2002).

Cancer cells often overexpress proteins that prevent the apoptotic cascade from being activated, including Bcl-2 and related anti-apoptotic proteins such as Bcl-xL, Mcl-1, A1/Bf1 and Bcl-w (Table 1) (Lowe and Lin, 2000). Targeting these proteins has become a strategy to inhibit cancer proliferation and promote cell death (Frenzel et al., 2009; Carneiro and El-Deiry, 2020). Developing cancer drugs targeting the apoptosis pathway represents the first

phase of clinical development in the field (Jan and Chaudhry, 2019). A comprehensive list of compounds targeting apoptotic pathways and demonstrating anti-cancer properties is presented in Table 2. ABT-737 was the initial chemical inhibitor targeting Bcl-2, Bcl-xL and Bcl-w (Del Gaizo Moore et al., 2007). It binds to the hydrophobic pocket of Bcl-2 family members and has shown efficacy against lung cancer, especially when combined with chemotherapy and radiation therapy. Navitoclax (ABT-263) demonstrates anti-cancer properties, particularly when used with MEK or tyrosine kinase inhibitors against solid tumors (Tse et al., 2008; Walensky et al., 2004) (ABT-199), a potent Bcl-2 inhibitor, has shown promising outcomes for treating acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL) (Souers et al., 2013). Selective Bcl-xL inhibitors include a vaccine for prostate cancer and ABBV-155,

TABLE 2 Apoptosis targeting drugs for cancer therapy.

Drug/Treatment	Mechanism of action	Cancer type	Clinical status	References
Venetoclax (ABT-199)	Selective BCL-2 inhibitor	Chronic lymphocytic leukemia, Acute myeloid leukemia	FDA Approved	DiNardo et al. (2019), Shimony et al. (2022)
Navitoclax (ABT-263)	BCL-2/BCL-XL inhibitor	Solid tumors, Hematological malignancies	Phase I/II	Tse et al. (2008), Gandhi et al. (2011), Rudin et al. (2012), Nor Hisam et al. (2021), Joly et al. (2022)
Obatoclax (GX15-070)	Pan-BCL-2 inhibitor	Hematological malignancies, Solid tumors	Phase I/II	Parikh et al. (2010), Paik et al. (2011), Goy et al. (2014)
ABT-737	BCL-2/BCL-XL/BCL-w inhibitor	Lung cancer, Hematological malignancies	Preclinical	Lee et al. (2022), Yuan et al. (2022), Yang et al. (2024)
Birinapant (TL32711)	SMAC mimetic (IAP antagonist)	Solid tumors, Hematological malignancies	Phase I/II	Amaravadi et al. (2015)
Nutlin-3	MDM2 inhibitor (p53 activator)	Leukemia, Solid tumors	Phase I	Secchiero et al. (2011)
RG7112	MDM2 inhibitor (p53 activator)	Sarcoma, myelogenous leukemia, hematologic neoplasms	Phase I	Andreoff et al. (2016)
Renieramycin T (RT)	Natural compound stabilizing p53	Lung cancer	Preclinical	Petsri et al. (2019)
Andrographolide (ANDRO)	Degrades mutant p53	Various cancers	Preclinical	Sato et al. (2018)
Protoporphyrin IX (PpIX)	Targets p53 and p73	Chronic lymphocytic leukemia	Preclinical	Son et al. (2019)
DJ34	Inhibits c-Myc, activates p53	Leukemia	Preclinical	Tadele et al. (2021)
AQ-101	MDM2 inhibitor	Leukemia	Preclinical	Gu et al. (2018)
Palbociclib	CDK4/6 inhibitor	Breast cancer	FDA Approved	Loi et al. (2022), Di Cosimo et al. (2023), Slamon et al. (2024)
Azacytidine	Hypomethylating agent	Myelodysplastic syndromes, Acute myeloid leukemia	FDA Approved	Mishra et al. (2023), Dohner et al. (2024) 11. Harper et al., 2023.
HO-3867	p53 agonist	Ovarian cancer	Preclinical	Devor et al. (2021)
SAHBA	Stapled peptide BH3 mimetic targeting BCL-XL	Leukemia	Preclinical	Chang et al. (2013)
SMBA1-3	Small molecules activating Bax	Various cancers	Preclinical	Li et al. (2017)
AMG 176 and AZD5991	MCL-1 inhibitor	Myeloma	Phase I	Caenepeel et al. (2018), Tron et al. (2018)
AM-8621	MCL-1 inhibitor	Hematological malignancies	Phase I	Wei et al. (2020)
VU661013 and S63845	MCL-1 inhibitor	Hematological malignancies,	Preclinical	Carneiro and El-Deiry (2020), Satta and Grant (2020)
LCL161	Oral SMAC mimetic (IAP antagonist)	Multiple myeloma, Breast cancer	Phase I/II	Yang et al. (2019)
Mapatumumab	TRAIL receptor agonist antibody (DR4)	Solid tumors	Phase II	Greco et al. (2008), Hotte et al. (2008), Trarbach et al. (2010), Younes et al. (2010), von Pawel et al. (2014), Ciuleanu et al. (2016)
Conatumumab	TRAIL receptor agonist antibody (DR5)	Solid tumors	Phase II	Herbst et al. (2010), Kindler et al. (2012)
Drozitumab	TRAIL receptor agonist antibody (DR5)	Solid tumors	Phase I/II	Rocha Lima et al. (2012)
APR-246 (Eprenetapopt)	Restores mutant p53 function	Myelodysplastic syndromes, Acute myeloid leukemia	Phase III	Lehmann et al. (2012), Cluzeau et al. (2021)
COTI-2	Restores mutant p53 function	Solid tumors	Phase I	Maleki Vareki et al. (2018), Lindemann et al. (2019), Nagourney et al. (2023), Tang et al. (2023)

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TABLE 2 (Continued) Apoptosis targeting drugs for cancer therapy.

Drug/Treatment	Mechanism of action	Cancer type	Clinical status	References
Panobinostat	HDAC inhibitor	Multiple myeloma	FDA Approved	23. San-Miguel et al., <i>Lancet Oncology</i> , 2014.
ABBV-075 (Mivebresib)	BET inhibitor	Solid tumors, Hematological malignancies	Phase I	Kim et al. (2018)
Mortaparib Plus	HSP70 inhibitor (p53 reactivator)	Colorectal cancer, Breast cancer	Preclinical	Sari et al. (2021)
ABBV-155 (Mirzotamab celzutoclax)	Antibody-drug conjugate targeting B7-H3	relapsed or refractory solid tumors	Phase I clinical trial	Walensky et al. (2004)

an antibody-drug conjugate being studied as monotherapy or for use in combination with taxanes for solid tumors (Walensky et al., 2004).

BH3 mimetics have been effectively created using stapled peptides that specifically bind through protein-protein interactions and have an improved ability to enter the cell (Ali et al., 2019). SAHBA (Stabilized Alpha-Helix of BCL-2 Domains) mimics the  $\alpha$ -helical BH3 section of proapoptotic BID, efficiently enters leukemia cells, binds to Bcl-xL, and promotes apoptosis (Chang et al., 2013). Targeting Bax using small molecules like SMBA1-3, which bind directly to Bax and inhibit the phosphorylation of S184, promotes cytochrome c release and apoptosis (Li et al., 2017).

The Bcl-2 family member Mcl-1 can prevent apoptosis induced by multiple apoptotic triggers such as radiation and chemotherapy (Wertz et al., 2011; Widden and Placzek, 2021). AM-8621 attaches to the Mcl-1 binding pocket, displaces BIM and induces apoptosis in a myeloma cell line (Wei et al., 2020). Derivatives AMG 176 and AZD5991 have shown notable outcomes in combination with venetoclax and chemotherapy (Caenepeel et al., 2018; Tron et al., 2018). Mcl-1 inhibitors VU661013 and S63845 show promise in treating blood cancers and overcoming resistance to venetoclax when used in combination with other therapies (Carneiro and El-Deiry, 2020; Satta and Grant, 2020). In addition, IAP inhibitors have been used to target apoptosis in cancer (Fulda and Vucic, 2012; Monian and Jiang, 2012). Antagonists like LCL161 and birinapant (TL32711) show promising anti-tumor effects, particularly in combination with chemotherapy, radiation and the immune checkpoint inhibitor (ICI) anti-PD1 pembrolizumab (Amaravadi et al., 2015; Yang et al., 2019).

Agonist antibodies were also created targeting DR4 and DR5 due to their favorable half-life and notable preclinical efficacy (Hymowitz et al., 1999; LeBlanc and Ashkenazi, 2003). The only clinically tested anti-DR4 monoclonal antibody is mapatumumab, a completely human DR4-agonistic antibody with selective and strong binding to DR4 and high cytotoxicity (Pukac et al., 2005). Mapatumumab was tested in phase I and II clinical trials for HCC, NSCLC, colorectal cancer, and refractory non-Hodgkin's lymphoma (Greco et al., 2008; Hotte et al., 2008; Trarbach et al., 2010; Younes et al., 2010; von Pawel et al., 2014; Ciuleanu et al., 2016), but none of the assays met the initial objectives, ending clinical development. Unlike DR4, several DR5 agonist antibodies have been developed and tested in clinic including Conatumumab, Drozitumab, Lexatumumab, LBY135, Tigatuzumab, and DS-8273a (Belyanskaya et al., 2007; Herbst et al., 2010; Kang et al., 2011;

Forero-Torres et al., 2013; Burvenich et al., 2016; Dominguez et al., 2017; Forero et al., 2017). Conatumumab and Drozitumab demonstrated efficacy in advanced solid tumors, while Lexatumumab was tested in prostate and bladder cancer cells (Shimada et al., 2007; Herbst et al., 2010; Rocha Lima et al., 2012). DS-8273a is the newest clinically tested anti-DR5 antibody. The initial study showed that DS-8273a might be used to eliminate myeloid-derived suppressor cells in advanced cancer patients, but no objective response was seen (Dominguez et al., 2017). It is tested in three more clinical trials to assess its safety in advanced solid tumors and lymphomas or its efficacy in combination with Nivolumab in advanced colorectal cancer and unresectable stage II and IV melanoma (Dubuisson and Micheau, 2017). In addition, chimeric mouse-human antibodies LBY135 and Tigatuzumab were developed. Solid advanced cancers tolerated LBY135 well, and Tigatuzumab was investigated for relapsed lymphoma or solid malignancies (Forero-Torres et al., 2010; Sharma et al., 2014). Conatumumab and Drozitumab reached phase II clinical trials, but Lexatumumab, LBY-135, and Tigatuzumab did not (Dubuisson and Micheau, 2017).

The p53 protein, a critical tumor suppressor, is often altered or deactivated in various malignancies, making it an ideal target for therapeutic treatments. Several p53-targeted medicines have been developed to help restore or improve p53 function. MDM2 inhibitors, including Nutlin-3, APG-115, RG7388, DS-3032, and MK-8242, suppress the p53-MDM2 interaction, stabilizing p53 and inducing apoptosis in malignancies such as gastric cancer and leukemia (Ding et al., 2013; Levine, 2022). Other MDM2 antagonists include AMG-232, HDM201, BI 907828, and ALRN-6924 (Carneiro and El-Deiry, 2020; Peng et al., 2022). MDMX inhibitors, such as XI-011 and DIMP53-1, restore p53 stability by inducing apoptosis and reducing migration in cervical and colon malignancies (Soares et al., 2017; Zhang J. et al., 2022). Small compounds such as PRIMA-1 (APR-017), APR-246 (Eprenetapopt), and COTI-2 restore mutant p53 to a functional state, reactivating its tumor-suppressive capabilities, with potential therapeutic uses in a variety of malignancies (Berke et al., 2022). The p53 agonist HO-3867 restores transcriptional repression in mutant p53, especially in ovarian cancer, resulting in cell death (Devor et al., 2021).

Cyclophilin A (CypA) inhibitors, such as HL001, impede MDM2-mediated p53 degradation, resulting in cell cycle arrest and death in NSCLC (Lu et al., 2017). Natural compounds such as Renieramycin T (RT) (Petsri et al., 2019) and Protopine (Son et al., 2019) stabilize p53, inducing apoptosis in lung and colon

tumors, respectively, whereas Andrographolide (ANDRO) degrades mutant p53 (Sato et al., 2018). Actinomycin V and TCCP also increase p53 expression, which causes apoptosis in many cancer cells (Lin S. Q. et al., 2019; Rashmi et al., 2019). Heat-shock protein inhibitors, such as Mortaparib (Plus), reactivate p53 by disrupting its association with mortalin, causing apoptosis in colorectal and breast malignancies (Sari et al., 2021). Furthermore, Protoporphyrin IX (PpIX) targets both p53 and its homolog p73, which promotes apoptosis in CLL (Son et al., 2019).

Novel therapeutics include gold complexes like MC3, which upregulate p53 via the ROS formation and have shown effectiveness in colorectal cancer (Dabiri et al., 2019), as well as platinum-based compounds like bromocoumarinplatin 1 and diplatin, which activate p53 to overcome cisplatin or carboplatin resistance respectively in lung cancer (Lin X. et al., 2019; Ma et al., 2020). Other small compounds, such as DJ34, kill leukemia stem cells by inhibiting c-Myc and activating p53 (Tadele et al., 2021), whereas AQ-101 inhibits MDM2 to activate p53 and increase apoptosis in leukemia (Gu et al., 2018).

Research is exploring inhibitors of uncontrolled oncogenic effectors such as PI3K, AKT,  $\beta$ -catenin, Myc, CDKs, mTOR, and VEGF (Sever and Brugge, 2015). CDK4/6 inhibitors like palbociclib enhance cell death and induce cell cycle arrest in various cancers (Tao et al., 2016). Epigenetic strategies focused on inducing apoptosis in cancer cells involve histone deacetylase (HDAC) inhibitors and Bromodomain and Extra-Terminal motif (BET) inhibitors (Bolden et al., 2006; Kim et al., 2018). HDAC inhibitors, such as panobinostat, enhance Noxa expression, reduce Mcl-1 levels, and increase sensitivity to Bcl-2 inhibitors (Liu et al., 2018). They also enhance the effectiveness of MEK inhibitors and venetoclax in treating multiple myeloma (DiNardo et al., 2019). BET inhibitors like ABBV-075, when combined with venetoclax, demonstrate promising outcomes in patients with cutaneous T cell lymphoma (CTCL) (Kim et al., 2018). The hypomethylating agent azacytidine, when combined with venetoclax and ABT-737, has shown promising results (Mishra et al., 2023).

## 1.2 Targeting autophagy for cancer therapy

Autophagy, a critical mechanism for maintaining cellular balance by removing damaged organelles and protein aggregates, can also facilitate cell death (Liu et al., 2023). Cells can undergo autophagy-related cell death in two primary ways: autophagy-dependent cell death (ADCD) which transpires independently of other programmed death mechanisms and autophagy-mediated cell death (AMCD) that occurs when autophagy-related molecules directly engage with those implicated in forms of cell death. (Zhou et al., 2022) (Figure 1). Moreover, autophagy is linked to other cell death mechanisms, such as apoptosis, necrosis, and ferroptosis, through a variety of processes (Dunkle and He, 2011; Gordy and He, 2012; Chen et al., 2018; Liu J. et al., 2020; Peng et al., 2022) (Figure 2).

Three distinct forms of autophagy have been identified: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) (Parzych and Klionsky, 2014). Microautophagy is a form of autophagy in which lytic organelles

autonomously engulf and degrade cytoplasmic components. It is essential for regulating biosynthesis, transport, metabolic adaptability, organelle remodeling, and the maintenance of cellular component quality (Saha et al., 2018). Macroautophagic autophagosomes convey cellular constituents for destruction to endosomes or lysosomes (Feng et al., 2014). Autophagy starts with an isolating membrane known as the phagophore, which encases a portion of the cytoplasm. The Atg9 protein promotes growth by supplying crucial lipid constituents. The Atg1 and Atg9 proteins, together with a phosphatidylinositol 3-kinase complex, govern this activity. In the subsequent phase, two conjugation steps transpire. The first activation entails Atg12 and the Atg7 protein. The Atg12 protein is conveyed to the Atg10 protein, leading to a covalent connection with Atg5. The Atg12-Atg5 complexes subsequently associate with the Atg16L protein. The ATG12-ATG5-ATG16L1 complex is essential for the production of autophagosomes. The second step of conjugation involves the proteins Atg3, Atg4, Atg7, and LC3. The Atg4 protease cleaves proLC3, resulting in the formation of LC3-I. Subsequently, the Atg7, Atg3, and Atg12-Atg5-Atg16L proteins are conjugated. The LC3-I protein interacts with the lipophilic phosphatidylethanolamine (PE) to generate the LC3-II form. These stages generate the autophagosome, which encapsulates a segment of the cytoplasm and proteins. The outer membrane of the autophagosome fuses with the lysosome to form an autophagolysosome. Lysosomal enzymes facilitate the digestion of the autophagolysosome's inner membrane and its contents (Gomez-Virgilio et al., 2022; Liu et al., 2023). Chaperone-mediated autophagy (CMA) removes damaged proteins during fasting or oxidative stress. The chaperone complex links the protein's target motif to facilitate lysosome trafficking. In the lysosome, the complex interacts with LAMP-2A's cytoplasmic tail and is destroyed (Bejarano and Cuervo, 2010).

Autophagy plays a complex role in cancer, acting as both an inhibitor and promoter of tumor growth (Chavez-Dominguez et al., 2020; Nawrocki et al., 2020; Debnath et al., 2023). It can help cancer cells avoid damage induced by chemotherapeutics and promote chemoresistance (Table 1) (Nawrocki et al., 2020; Debnath et al., 2023). Preclinical research using chemotherapeutics like cyclophosphamide, imatinib, and vorinostat has shown that autophagy reduces the effectiveness of these drugs and contributes to acquired resistance (Mele et al., 2020). Furthermore, autophagy aids cancer cells in adapting to chemotherapy (Ahmadi-Dehlaghi et al., 2023).

Autophagy inhibitors have shown promise in combination with chemotherapeutic and targeted immunotherapeutic drugs (Table 3). While many prospective autophagy inhibitors are being developed, chloroquine (CQ) and its derivative hydroxychloroquine (HCQ) are the only approved drugs (Wang et al., 2011). HCQ, like CQ, suppresses autophagy by blocking lysosomal acidification and autophagosome degradation but has lower toxicity (Sui et al., 2013; Cook et al., 2014; Pellegrini et al., 2014; Lee et al., 2015). A Phase II trial for muscle-invasive bladder cancer is investigating the combination of HCQ with gemcitabine and cisplatin for systemic chemotherapy (Ojha et al., 2016). Similarly, in breast cancer, HCQ combined with tamoxifen was found more effective in suppressing autophagy in estrogen-positive (ER+) cell lines (Cook et al., 2014). In renal cell carcinoma, HCQ combined with temsirolimus led to



TABLE 3 Autophagy targeting drugs for cancer therapy.

Drug/Compound	Mechanism of action	Cancer type	Clinical status	References
Chloroquine (CQ)	Inhibits autophagy by blocking autophagosome-lysosome fusion	Various Solid Tumors, Glioblastoma, Pancreatic Cancer	FDA Approved for Malaria; Clinical Trials in Cancer	Varisli et al. (2020), Agalakova (2024)
Hydroxychloroquine (HCQ)	Inhibits autophagy by preventing lysosomal acidification	Bladder Cancer, Breast Cancer, Renal Cell Carcinoma, Multiple Myeloma, Melanoma	FDA Approved for Malaria and RA; Clinical Trials in Cancer	Sui et al. (2013), Cook et al. (2014), Pellegrini et al. (2014), Lee et al. (2015)
HCQ + Gemcitabine and Cisplatin	HCQ inhibits autophagy, potentially enhancing chemotherapy effectiveness	Muscle-Invasive Bladder Cancer	Phase II Clinical Trials	Ojha et al. (2016)
HCQ + Tamoxifen	HCQ inhibits autophagy, enhancing efficacy of tamoxifen in ER + breast cancer	Breast Cancer (ER+)	Preclinical/Clinical Trials	Cook et al. (2014)
HCQ + Temsirolimus	HCQ inhibits autophagy, increasing apoptosis when combined with mTOR inhibitor	Renal Cell Carcinoma	Phase I Clinical Trials	Lee et al. (2015)
HCQ + Bortezomib	HCQ inhibits autophagy, enhancing proteasome inhibitor efficacy	Multiple Myeloma	Phase I/II Clinical Trials	Vogl et al. (2014)
HCQ + Temozolomide	HCQ inhibits autophagy, enhancing chemotherapy effectiveness	Advanced Solid Tumors and Melanoma	Phase I/II Clinical Trials	Cheng et al. (2009), Rangwala et al. (2014b)
HCQ + Rapamycin	HCQ inhibits autophagy; rapamycin induces autophagy via mTOR inhibition	Advanced Solid Tumors	Phase I Clinical Trials	Rangwala et al. (2014a)
SBI-0206965	ULK1 inhibitor blocking autophagy initiation	Various Cancers	Preclinical	Tang et al. (2017)
Bafilomycin A1	Inhibits vacuolar H (+)-ATPase (V-ATPase), preventing autophagosome-lysosome fusion	Various Cancers	Preclinical	Lu et al. (2015)
Rapamycin (Sirolimus)	Activates autophagy via mTOR inhibition	Renal Cell Carcinoma, Breast Cancer	FDA Approved for Organ Transplant Rejection; Investigational in Cancer	Blagosklonny (2023), Li et al. (2024c)
Everolimus (RAD001)	mTOR inhibitor inducing autophagy	Renal Cell Carcinoma, Breast Cancer, Neuroendocrine Tumors	FDA Approved for RCC, Breast Cancer	Motzer et al. (2008), Singh et al. (2014), Chen et al. (2019)
Temsirolimus (CCI-779)	mTOR inhibitor inducing autophagy	Various Cancers	FDA Approved for RCC	Harshman et al. (2014), Zanardi et al. (2015)
BEZ235 (Dactolisib)	Dual PI3K/mTOR inhibitor inducing autophagy	Breast Cancer, Glioblastoma	Phase I/II Clinical Trials	Wise-Draper et al. (2017), Salazar et al. (2018)
Sunitinib	Induces autophagy via inhibition of multiple tyrosine kinases	Renal Cell Carcinoma, GIST	FDA Approved	Vuorinen et al. (2019), Lara et al. (2024)
Vorinostat (SAHA)	HDAC inhibitor inducing autophagy	Cutaneous T-cell Lymphoma, Solid Tumors	FDA Approved for CTCL; Investigational in other cancers	Mann et al. (2007), Mahalingam et al. (2014)
Arsenic Trioxide (ATO)	Induces autophagy via oxidative stress	Acute Promyelocytic Leukemia, Multiple Myeloma	FDA Approved for Acute promyelocytic leukemia; Investigational in other cancers	Jiang et al. (2023), Gill (2024)
Vitamin D Analogs (e.g., Calcitriol)	Induce autophagy through modulation of AMPK/mTOR pathway	Prostate Cancer, Breast Cancer	Preclinical/Clinical Trials	Duffy et al. (2017), Jeon and Shin (2018)
Metformin	Activates AMPK, inducing autophagy	Breast Cancer, Prostate Cancer, Colorectal Cancer	FDA Approved for Type 2 Diabetes; Investigational in cancer	Kasznicki et al. (2014), Hua et al. (2023)
Chlorpromazine	Antipsychotic drug inhibiting autophagy by interfering with lysosomal function	Glioblastoma, Lung Cancer	Preclinical	Kamgar-Dayhoff and Brelidze (2021), Matteoni et al. (2021)

(Continued on following page)

TABLE 3 (Continued) Autophagy targeting drugs for cancer therapy.

Drug/Compound	Mechanism of action	Cancer type	Clinical status	References
3-Methyladenine (3-MA)	PI3K inhibitor blocking autophagy initiation	Various Cancers <i>in vitro</i>	Preclinical	Zhang et al. (2022e)
Silibinin	Natural compound inducing autophagy via modulation of PI3K/Akt/mTOR pathway	Prostate Cancer, Breast Cancer	Preclinical	Chatran et al. (2018)
Resveratrol	Induces autophagy through SIRT1 activation and mTOR inhibition	Various Cancers	Preclinical/Clinical Trials	Song et al. (2023)
Curcumin	Natural compound inducing autophagy via multiple pathways	Breast Cancer, Colon Cancer	Preclinical/Clinical Trials	Zhao et al. (2016), Saghatelian et al. (2020), Deng et al. (2024)
Autophinib	Selective ULK1 inhibitor blocking autophagy initiation	Various Cancers <i>in vitro</i>	Preclinical	Aleksandrova and Suvorova (2023)
Veru-111 (Sabizabulin)	Microtubule disruptor inducing autophagy and apoptosis	Prostate Cancer, Breast Cancer	Phase II/III Clinical Trials	Krutilina et al. (2022), Markowski et al. (2022)
SBI-0206965	ULK1 inhibitor blocking autophagy initiation	Various Cancers	Preclinical	Tang et al. (2017)
Spautin-1	Beclin-1 inhibitor promoting Vps34 complex degradation	Various Cancers	Preclinical	Kona and Kalivendi (2024)
SAR405	Vps34 kinase inhibitor blocking autophagy initiation	Various Cancers	Preclinical	Pasquier (2015)
Gambogic Acid	Induces caspase-mediated cleavage of autophagy proteins, inhibiting autophagy	Various Cancers	Preclinical	Ishaq et al. (2014)
ATG4 Inhibitors (NSC185058, NSC377071)	Inhibit ATG4B protease, blocking autophagy	Various Cancers	Preclinical	Akin et al. (2014)
Verteporfin	Inhibits early-stage autophagosome formation	Pancreatic Cancer, Glioblastoma	FDA Approved for Macular Degeneration; Investigational in Preclinical Cancer Studies	Donohue et al. (2011)
Lysosomal Inhibitors (ROC325, Lys05, DQ661, DC661)	Inhibit lysosomal function, blocking autophagic flux	Various Cancers	Preclinical	Amaravadi and Winkler (2012), Rebecca et al. (2017), Nawrocki et al. (2019), Rebecca et al. (2019)
Z-DEVD (Caspase-3 Inhibitor) + RAD001 + Irradiation	Induce autophagy by inhibiting apoptosis and mTOR, enhancing radiation-induced autophagy	Non-Small Cell Lung Cancer	Preclinical	Kim et al. (2008)
Silver Nanoparticles (AgNPs)	Induce autophagy; effect confirmed with autophagy inhibitor 3-MA	Glioma	Preclinical	Wu et al. (2015)

increased apoptosis by inhibiting autophagy (Lee et al., 2015). Early phase I/II trials of HCQ have focused on adult solid tumors, including pancreatic adenocarcinoma, melanoma, colorectal carcinoma, myeloma, lymphoma and renal cell carcinoma, using chemotherapy drugs such as temsirolimus, bortezomib, temozolomide, vorinostat, and doxorubicin (Llovet et al., 2008; Mahalingam et al., 2014; Rangwala et al., 2014a; Rangwala et al., 2014b; Rosenfeld et al., 2014; Vogl et al., 2014; Wolpin et al., 2014). HCQ doses ranged from 400 mg to 600 mg twice daily, showing tolerability with partial responses and stable disease in some patients (Carew and Nawrocki, 2017). For advanced solid tumors and melanoma, HCQ combined with 150 mg/m<sup>2</sup> of temozolomide showed 27% stable disease and 14% partial response in wildtype melanoma (Cheng et al., 2009; Rangwala et al., 2014b). The combination of HCQ and rapamycin, an inhibitor of

mTORC1 activity, was well-tolerated in advanced solid tumor (Rangwala et al., 2014a). In myeloma, HCQ combined with bortezomib improved the efficiency of proteasome inhibitors by causing the accumulation of misfolded proteins, with 45% of patients showing stable disease. The most common adverse effects were gastrointestinal issues and cytopenias (Vogl et al., 2014).

Autophagy activation by drugs like sorafenib, a multi-tyrosine kinase mTOR inhibitor used for hepatocellular cancer, is being explored as a potential cause of drug resistance (Llovet et al., 2008). Clinical trials have investigated HCQ in hepatocellular cancer (Cheng et al., 2009) and targeted immunotherapeutic treatments, such as checkpoint inhibitors, have limited efficacy and high costs. Combining autophagy modulators like HCQ with immune checkpoint inhibitors (ICI) has the potential to improve efficacy and reduce treatment costs. Several inhibitors targeting different

stages of autophagy are under investigation including inhibitors of upstream signaling molecules: SBI-0206965 (ULK1 inhibitor) (Tang et al., 2017), Spautin-1 (Beclin1 inhibitor), SAR405 (Vps18 kinase inhibitor), and gambogic acid (induces caspase-mediated cleavage of autophagy proteins) (Ishaq et al., 2014; Pasquier, 2015). Autophagy initiation inhibitors include ATG4 inhibitors NSC185058 and NSC377071, and Verteporfin (inhibits early-stage autophagosome formation) (Donohue et al., 2011; Akin et al., 2014). Lysosomal inhibitors include ROC325 (Nawrocki et al., 2019), Lys05 (Amaravadi and Winkler, 2012), DQ661 (Rebecca et al., 2017), and DC661 (Rebecca et al., 2019).

Preclinical trials have also explored autophagy's potential to enhance radiation therapy (Kim et al., 2008; Kuwahara et al., 2011). For example, in a lung cancer mouse model, combining Z-DEVD (caspase-3 inhibitor), RAD001 (mTOR inhibitor), and irradiation induced the highest levels of autophagy and associated radiation damage. This suggests that inhibiting both apoptosis and mTOR during radiotherapy could improve outcomes in non-small cell lung cancer patients (Kim et al., 2008). Similarly, in glioma cells, autophagy induction by silver nanoparticles (AgNPs) and/or radiation was confirmed by applying 3-methyladenine (3-MA), highlighting selective autophagy as a promising therapeutic avenue for effective cancer treatment (Wu et al., 2015).

### 1.3 Necroptosis in cancer development and treatment

Programmed inflammatory cell death, known as necroptosis, was first identified as an alternative to apoptosis following the activation of death domain receptors (Degterev et al., 2005; Dhuriya and Sharma, 2018) (Figure 1). Necroptosis is a regulated type of necrosis that is dependent on receptor interacting kinase-1 (RIPK1) and RIPK3 phosphorylating mixed-lineage kinase-like (MLKL) (Vandenabeele et al., 2010; Sun et al., 2012; Newton et al., 2014) (Figure 2). The necroptotic process begins when RNA- and DNA-sensing molecules and cell surface death receptors including FasRs, TNFR1, IFN receptors, and TLRs are activated (Kaiser et al., 2013). There are two ways that cell death signaling continues (Pasparakis and Vandenabeele, 2015). Complex I, a survival complex that communicates via NF- $\kappa$ B, can be created by TNF- $\alpha$ . RIPK1 deubiquitination transforms the complex into apoptotic complex IIa. When caspase-8 is absent and RIPK3 is elevated, the complex forms IIb (the necrosome). The death domain-related proteins RPK1, RPK3, and Fas on this necrosome directly phosphorylate the kinase domain-like protein (MLKL) to induce necroptosis. MLKL phosphorylation forms an oligomer that punctures the plasma membrane, killing the cell. Calmodulin-dependent protein kinase and mitochondrial serine/threonine protein phosphatase II are other RIPK3 downstream effects (He et al., 2009; Cai et al., 2014; Wang et al., 2014; Murphy, 2020). Necroptotic cell death is characterized by cell membrane perforation, elevated intracellular osmotic pressure, cell rounding and swelling, organelle swelling, impaired mitochondrial activity, mitochondrial membrane potential loss, nuclear chromatin loss, and plasma membrane rupture (Dhuriya and Sharma, 2018). Plasma membrane rupture causes potassium efflux, cytokines, and chemokines, which cause inflammation and immunological responses (Dhuriya and Sharma, 2018).

Necroptosis is involved in various aspects of tumor biology, including tumor development, necrosis, metastasis and the immune response within tumors (Najafiov et al., 2017; Gong et al., 2019; Yan et al., 2022; Meier et al., 2024). This cell death pathway exhibits both pro- and anti-tumorigenic effects (Ye et al., 2023). Major regulators of necroptosis are often downregulated in cancer cells, correlating with unfavorable outcomes (Table 1) (Yan et al., 2022). Necroptosis has emerged as a novel target for anticancer therapy due to its significant role in tumor biology (Gong et al., 2019).

Several natural compounds and small molecule inhibitors are known to induce necroptosis in cancer cells (listed in Table 4) (Wu et al., 2020). Chloroquine increases the expression of endogenous RIPK3 in colorectal cancer cell lines, with necroptosis being the mechanism (Meng et al., 2016). Shikonin, derived from a Chinese medicinal herb, induces necroptosis in nasopharyngeal carcinoma cells by enhancing reactive oxygen species (ROS) production and increasing RIPK1, RIPK3 and MLKL expression (Liu et al., 2019). Emodin triggers necroptosis in glioma cell lines by activating the TNF/RIPK1/RIPK3 pathway (Zhou et al., 2020). Neoalbacinol (NA), a compound derived from the fungus *Albatrellus confluens*, has been found to trigger necroptosis by facilitating the autocrine release of TNF $\alpha$  through the modulation of the RIPK/NF- $\kappa$ B signaling pathway and RIPK3-dependent reactive oxygen species (ROS) generation (Yu et al., 2015). The steroid glycoside Ophiopogonin D induces necroptosis in prostate cancer cells by activating RIPK1 (Lu et al., 2020). Resibufogenin inhibits colorectal cancer cell line growth by increasing RIPK3 expression (Han et al., 2018). The initiation of necroptosis can also be influenced by adjusting upstream signaling pathways, such as using the sphingosine analog FTY720 (fingolimod), which triggers necroptosis in human lung cancer cells by interacting with the I2PP2A/SET oncoprotein and activating the PP2A/RIPK1 pathway (Saddoughi et al., 2013).

Nanoparticles to induce necroptosis in cancer cells is another emerging field (Mohammadinejad et al., 2019). Although the antifungal agent Shikonin shows potential, its clinical use is limited due to poor tumor specificity, low water solubility, short bloodstream half-life, and high risk of side effects on healthy tissues (Boulos et al., 2019). To address these issues, Feng et al. developed an Fe(III)-shikonin supramolecular nanomedicine (FSSN) using metal-polyphenol coordination of Fe(III) and shikonin, demonstrating improved water solubility and reduced cytotoxicity in normal cells and induced both ferroptosis and necroptosis (Feng et al., 2022). In CT26 colon cancer cells, graphene oxide nanoparticles triggered necroptosis by enhancing RIPK1, RIPK3, and HMGB1 activity (Chen et al., 2015). Similarly, selenium nanoparticles induced necroptosis in prostate adenocarcinoma cells by increasing ROS production and TNF and interferon regulatory factor 1 expression (Sonkusre, 2019). Folate-sodium alginate-cholesterol nanoparticles delivering doxorubicin and metformin achieved targeted accumulation and induced various forms of programmed cell death, including necroptosis, apoptosis, and pyroptosis in xenograft melanoma tumors (Song et al., 2021). Myricetin-loaded solid lipid nanoparticles (MYC-SLNs) enhanced necroptosis in A549 cells by increasing RIPK3 and MLKL expression without affecting apoptosis and without apparent effects on the growth and health of MRC5 cells (Alidadi et al., 2022). Ma et al. developed star-PCL-azo-PEG micelles (sPCPEG-azo) to deliver

TABLE 4 Necroptosis targeting drugs for cancer therapy.

Drug/Compound	Mechanism of action	Cancer type	Clinical status	References
Chloroquine	Increases expression of RIPK3	Colorectal Cancer	FDA Approved for Malaria; Investigational in cancer	<a href="#">Meng et al. (2016)</a>
Shikonin	ROS production and upregulation of RIPK1, RIPK3, MLKL	Nasopharyngeal Carcinoma, Various Cancers	Preclinical	<a href="#">Han et al. (2007)</a> , <a href="#">Boulos et al. (2019)</a> , <a href="#">Liu et al. (2019)</a>
Emodin	activation of TNF $\alpha$ /RIPK1/RIPK3 pathway	Glioma, Various Cancers	Preclinical	<a href="#">Zhou et al. (2020)</a> , <a href="#">Sharifi-Rad et al. (2022)</a>
Neolbaconol (NA)	modulation of RIPK/NF- $\kappa$ B pathway and RIPK3-dependent ROS generation	Breast Cancer	Preclinical	<a href="#">Yu et al. (2015)</a>
Ophiopogonin D	activates RIPK1	Prostate Cancer	Preclinical	<a href="#">Lu et al. (2020)</a>
Resibufogenin	increasing RIPK3 expression,	Colorectal Cancer	Preclinical	<a href="#">Han et al. (2018)</a>
FTY720 (Fingolimod)	I2PP2A/SET oncoprotein interaction and activation of PP2A/RIPK1 pathway	Lung Cancer	FDA Approved for Multiple Sclerosis; Investigational in cancer	<a href="#">Saddoughi et al. (2013)</a>
Fe(III)-Shikonin Supramolecular Nanomedicine (FSSN)	Induces necroptosis and ferroptosis; improved delivery and reduced toxicity	Colon Cancer	Preclinical	<a href="#">Feng et al. (2022)</a>
Graphene Oxide Nanoparticles	enhances RIPK1, RIPK3, and HMGB1 activity	Colon Cancer	Preclinical	<a href="#">Chen et al. (2015)</a>
Selenium Nanoparticles	increased ROS production and upregulation of TNF $\alpha$ and IRF1	Prostate Cancer	Preclinical	<a href="#">Sonkusre (2019)</a>
Myricetin-loaded Solid Lipid Nanoparticles (MYC-SLNs)	increases RIPK3 and MLKL expression	Lung Cancer (A549 cells)	Preclinical	<a href="#">Alidadi et al. (2022)</a>
Dimethyl Fumarate (Delivered via sPCPEG-azo Micelles)	depletes GSH, increasing ROS levels, activating MAPKs	Colon Cancer	Preclinical	<a href="#">Ma et al. (2016c)</a>
Necrosulfonamide (NSA)	MLKL inhibitor;	Various Cancers	Preclinical	<a href="#">Liu et al. (2016)</a>
Necrostatin-1	RIPK1 inhibitor	Colorectal Cancer	Preclinical	<a href="#">Liu et al. (2015)</a> , <a href="#">Cao and Mu (2021)</a>
GSK2982772	RIPK1 inhibitor	Approved for Inflammatory Diseases; investigational in Cancer	Phase IIa Clinical Trials (Inflammatory Diseases)	<a href="#">Wu et al. (2020)</a> , <a href="#">Tong et al. (2022)</a>
Trichothecin	increases RIPK3 expression, enhancing MLKL phosphorylation, activating ROS production	Chemoresistant Cancers	Preclinical	<a href="#">Zhao et al. (2021b)</a>
CBL0137	Induces Z-type dsDNA formation, activating ZBP1-dependent necroptosis; reverses insensitivity to immune checkpoint inhibitors	Melanoma	Preclinical	<a href="#">Zhang et al. (2022c)</a>

dimethyl fumarate (DMF) specifically to the colon, inducing necroptosis by eliminating GSH, increasing ROS levels and activating MAPKs ([Ma Z. G. et al., 2016](#)).

In a study conducted by [Liu et al.](#), MLKL inhibitor necrosulfonamide (NSA) was shown to significantly delay tumor growth, thus offering compelling evidence of the role necroptosis plays in promoting tumor development ([Liu et al., 2016](#)). In mice, the use of necrostatin-1, another necroptosis inhibitor, has been found to be effective in reducing colitis-associated tumorigenesis ([Liu et al., 2015](#)). There is ongoing testing of the RIPK1 inhibitor, GSK2982772, in phase 2a clinical studies for individuals with inflammatory disease. Furthermore, in a clinical trial

(NCT04739618), researchers explored the potential benefits of nonablative cryosurgical freezing-induced necroptosis followed by immunotherapeutic drug injection in metastatic solid tumors. The immunotherapy included pembrolizumab (anti-PD1), ipilimumab (anti-CTLA-4), and GM-CSF. The aim was to assess the overall response rate of radiographic changes ([Tong et al., 2022](#)). In addition, induction of apoptosis has also been shown to reverse drug resistance. [Xu Zhao et al.](#), effectively employed trichothecin to trigger necroptosis in cancers that are resistant to chemotherapy. Mechanistically, the natural secondary metabolite trichothecin significantly increased the expression of RIPK3. Subsequently, RIPK3 enhanced the phosphorylation of MLKL and activated

mitochondrial energy metabolism and ROS production. This novel approach sensitizes cancer cells to cisplatin therapy (Zhao X. et al., 2021).

In addition, it has been shown that necroptosis-inducing drugs could impact the effectiveness of ICIs in individuals with cancer (Tang et al., 2020). Using a viral vaccination strategy, Hoecke et al. were able to effectively deliver the necroptosis mediator MLKL to tumor cells, resulting in the promotion of necroptotic death and the enhancement of antitumor immunity. Increased immunity directly against neo-epitopes was responsible for the potent antitumor immunity (Van Hoecke et al., 2020). In addition, the RNA editing enzyme ADAR1 has been widely recognized for its role in suppressing Z-type dsRNA, a substrate for ZBP1. This suppression mechanism leads to resistance and limited responsiveness to ICIs (Zhang T. et al., 2022). However, the small-molecule drug CBL0137 has the ability to directly induce the formation of Z-type dsDNA in cells. This in turn activates ZBP1-dependent necroptosis and effectively reverses the insensitivity to ICIs in mouse melanoma models (Zhang T. et al., 2022). In addition, cIAPs have the ability to hinder the RIPK1-dependent necroptosis process. However, this inhibition can be counteracted by Smac mimetics which then trigger the activation of the necroptotic death pathway in Burkitt's lymphoma cell lines (Koch et al., 2021). In melanoma, the response to ICIs can be enhanced by using Smac mimetics which have a direct impact on immune cells such as B cells, MDSCs, DCs, and cytotoxic T cells (Michie et al., 2020). Based on the evidence, it appears that necroptosis could potentially be employed to enhance the readiness of the tumor microenvironment for immunotherapy.

Even with progress in necroptosis research, various obstacles impede its application in cancer treatment. The practicality of necroptosis, having potential as an alternative therapy for tumors resistant to apoptosis, continues to be debated. Hitomi et al. (2008) identified a cellular signaling network that regulated necroptosis and implicated two suppressor genes, CYLD and EDD1, and four Ras-related proteins, suggesting a role in tumorigenesis. CYLD gene mutations in tumorigenic epidermal cells promote carcinoma aggressiveness by increasing angiogenic factor production, which is crucial to epidermal cancer malignancy (Alameda et al., 2010). RIPK3 and CYLD were downregulated in CLL cells, and LEF1 represses CYLD. Together, necroptosis may be crucial to carcinogenesis (Reed, 2006). Tumor heterogeneity presents a significant challenge, as numerous cancers are deficient or have mutated for essential necroptosis regulators such as RIPK3 or MLKL, which restricts the effectiveness of necroptosis inducers. RIPK3-r, a truncated splice variation of RIPK3, was dramatically elevated in colon and lung tumors compared to matched normal tissues, suggesting that it may be a primary splice form involved in carcinogenesis, according to Yang et al. (2005). The RIPK3 gene lies on chromosome 14q11.2, which is mutated in several malignancies, including nasopharyngeal carcinoma and T cell leukemia/lymphoma (Kasof et al., 2000). In non-Hodgkin lymphoma, RIPK3 gene polymorphisms increases tumor risk (Wu et al., 2012). Furthermore, existing inducers exhibit a lack of selectivity, resulting in uncontrolled inflammation and the possibility of harming healthy tissues, which raises concerns regarding off-target effects and systemic toxicity. Necroptosis may enhance anti-tumor immunity due to its pro-inflammatory characteristics,

yet it also has the potential to facilitate tumor progression by creating a pro-tumor environment. Necroptosis of tumor cells can affect the TME in a way that can contribute to tumor growth because the inflammation associated with necroptosis can stimulate cell division, genetic instability, angiogenesis and metastasis (Negroni et al., 2020). Furthermore, the restricted clinical evidence, primarily based on preclinical models, along with the unpredictable nature of necroptosis outcomes, adds to the complexity of its application. Tumors can develop resistance to necroptosis, similar to how they respond to therapies that induce apoptosis. Consequently, additional research is essential to enhance targeting specificity, reduce inflammatory risks, and confirm the efficacy of necroptosis-based treatments in clinical environments.

## 1.4 The roles of pyroptosis in cancer cell survival and treatment strategies

Pyroptosis is a form of RCD associated with inflammatory responses. It is triggered by human caspase-1, -3, -4, -5 (mouse caspase-11), -6, -8, and -9 and NLRP3 and has significant therapeutic implications for several malignancies due to its profound effects on the invasion, proliferation, and metastasis of tumor cells (Table 1) (Shi J. et al., 2014; Fang et al., 2020; Zheng and Li, 2020; Rao et al., 2022; Wei et al., 2022) (Figure 1). Gasdermin (GSDM) superfamily members, GSDMA-GSDME, which are essential to pyroptosis, are triggered by caspases and perforate the plasma membrane (Kayagaki et al., 2015; Shi et al., 2015; Rogers et al., 2019) (Figure 2). The characteristic features of pyroptosis in cancer involve gasdermins family protein cleavage and polymerization, both N-terminal and C-terminal junction domain cleavage, and activated N-terminal regions. The N-terminal generates a cell membrane pore by binding to membrane lipids, phosphatidylinositol, and cardiolipin, causing cell osmotic swelling, plasma membrane rupture, and death (Ding et al., 2016; Feng et al., 2018). Gasdermins create 10–20 nm holes in cell membranes, releasing cell contents slowly and potentially causing inflammatory responses. The cells become flattened eventually and create 1–5  $\mu\text{m}$  apoptotic body-like protrusions. Nuclear concentration and chromatin DNA breaking occur as cells enlarge to rupture plasma membrane (Zhang et al., 2018). Pyroptotic pathway can occur either through classical or non-classical pathway in cancer. The classical pathway is activated by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) (Chen and Nunez, 2010; Franchi et al., 2012). Cytoplasmic pattern recognition receptors (PRRs) identify them. Based on particular inputs, nod-like receptors (NLRs) or melanoma deficiency factor 2-like receptors (ALRs) produce inflammatory bodies and activate caspase-1. After Caspase-1 cleaves GSDMD, its N-terminal aggregates into cell membrane holes (Amarante-Mendes et al., 2018; Zheng D. et al., 2020) (Figure 2). Additionally, caspase-1 cleaves pro-IL-1 $\beta$  and pro-IL-18 into mature IL-1 $\beta$  and IL-18, which are then released via the membrane hole. The non-classical pyrolytic pathway requires caspase-4/-5/-11 activation. After lipopolysaccharide (LPS) stimulates the cytoplasm, caspase-4/caspase-5/caspase-11 (the human equivalent of mouse caspase-11 caspase-4/caspase-5) can directly bind to the conserved structure of LPS, lipoprotein A,

TABLE 5 Pyroptosis targeting drugs for cancer therapy.

Drug/Compound	Mechanism of action	Cancer type	Clinical status	References
Cisplatin (DDP)	Induces pyroptosis via activation of GSDME through caspase-3	Various Cancers (e.g., gastric, esophageal)	FDA Approved Chemotherapy Agent	Yan et al. (2021), Xuzhang et al. (2024), Wang et al. (2018b) <sup>1</sup> , Wu et al. (2019a) <sup>2</sup>
5-Fluorouracil (5-FU)	Triggers pyroptosis via GSDME activation	Gastric Cancer, Colorectal Cancer	FDA Approved Chemotherapy Agent	Yu and He (2017), Wang et al. (2018b)
Paclitaxel	Induces pyroptosis through GSDME activation	Various Solid Tumors	FDA Approved Chemotherapy Agent	Zhang et al. (2019a)
Lobaplatin	Induces pyroptosis via ROS/JNK/BAX pathway activating caspase-3/9 and GSDME	Cervical Cancer, Colorectal Cancer	Approved in China; Investigational elsewhere	Yu et al. (2019), Chen et al. (2022)
Atezolizumab	Induces pyroptosis when combined with chemotherapy/radiation	Non-Small Cell Lung Cancer	FDA Approved	Wang et al. (2022d)
Trimethylamine N-oxide (TMAO)	Triggers GSDME-mediated pyroptosis; enhances anti-PD-1 effects	Breast Cancer	Preclinical	Wang et al. (2022a), Jia et al. (2023)
Val-boroPro (Talabostat)	Activates CARD8 inflammasome, leading to caspase-1 activation and pyroptosis	Acute Myeloid Leukemia (AML)	Clinical trials halted after Phase II	Johnson et al. (2018)
BRAF Inhibitors (BRAFi) and MEK Inhibitors (MEKi)	Induce pyroptosis via GSDME activation when combined	Melanoma	FDA Approved (both agents separately); Combination approved	Erkes et al. (2020)
BI2536 (PLK1 Inhibitor) with Cisplatin	Combination induces pyroptosis via caspase-3/GSDME pathway	Esophageal Cancer	Preclinical	Wu et al. (2019a)
Ivermectin	Activates pannexin-1 pathway, leading to pyroptosis via P2X4/P2X7 receptors	Triple-Negative Breast Cancer	FDA Approved for Parasitic Infections; Investigational in cancer	Draganov et al. (2015)
Metformin	Triggers GSDMD-mediated pyroptosis via AMPK/NLRP3 pathway	Various Cancers	FDA Approved for Type 2 Diabetes; Investigational in cancer	Pizato et al. (2018), Zheng et al. (2020c)
Anthocyanin	Induces GSDMD-mediated pyroptosis	Breast Cancer	Dietary Supplement (Preclinical in cancer)	Yue et al. (2019)
Docosahexaenoic Acid (DHA)	Triggers pyroptosis via GSDMD activation	Colon Cancer	Dietary Supplement (Preclinical in cancer)	Wang et al. (2019a), Wang et al. (2019a) <sup>18</sup>

causing oligomerization, activation, and the N-terminal of GSDMD to be cleaved and localized to the cell membrane to form membrane pores (Kayagaki et al., 2015). Pyroptosis is quicker and more violent than apoptosis, releasing several pro-inflammatory molecules. Cell scorch is caused by inflammatory corpuscles and GSDM family proteins.

Several chemotherapeutic drugs, including cisplatin, paclitaxel, 5-FU, lobaplatin and others have been found to trigger pyroptosis in tumor cells (Table 5) (Zhang C. C. et al., 2019; Jia et al., 2023). Chemotherapy-induced pyroptosis is frequently the result of GSDME pathway activation. Chemotherapy drug Lobaplatin triggers pyroptosis in cervical cancer and colorectal cancer by activating GSDME (Chen et al., 2022). This effect is achieved by activating caspase-3/9 through the ROS/JNK/BAX mitochondrial apoptosis pathway (Yu et al., 2019). 5-FU triggers pyroptosis in gastric cancer cells via GSDME instead of GSDMD (Wang Y. et al., 2018). When exposed to cisplatin or 5-FU, GSDME<sup>+/+</sup> mice experience significant intestinal damage and infiltration of immune cells. On the other hand, GSDME<sup>-/-</sup> mice show less injury, indicating that triggering pyroptosis in cancer cells might offer a potential alternative approach for cancer treatment (Yu and He, 2017).

Clinical trials have demonstrated that the combination of PD-L1 inhibitors with chemotherapy or radiation can effectively eliminate tumor cells through pyroptosis induction (Reck et al., 2019). This approach has shown promising results in terms of improved patient survival rates, surpassing those observed in patients solely treated with PD-L1 inhibitors. In breast cancer cells, the presence of Trimethylamine N-oxide (TMAO) can trigger GSDME-mediated pyroptosis (Wang H. et al., 2022), and when TMAO is combined with PD-1, it has the potential to enhance the antitumor effects of anti-PD-1 (Jia et al., 2023).

CAR-T cells have been successfully utilized to effectively treat hematological malignancies, yielding favorable outcomes (Gill and Brudno, 2021). However, cytokine release syndrome (CRS) is a significant side effect of this technology. When CAR-T cells release granzyme B, it can trigger pyroptosis by activating the caspase-3/GSDME pathway (Liu Y. et al., 2020). Interestingly, the elimination of GSDME through knockout has been found to effectively prevent CRS. Furthermore, the presence of perforin/granzyme B in CAR-T cells, as opposed to in CD8<sup>+</sup> T cells, triggers GSDME-mediated pyroptosis in target cells (Liu Y. et al., 2020). These findings underscore the clinical importance of pyroptosis in immunotherapy. The release of IL-1 $\beta$  and IL-18 by pyroptotic

cells, along with other DAMPs, can attract immune cells like dendritic cells (DCs) and macrophages (MFs) to engulf the pyroptotic cells (Wang Q. et al., 2018; Karki and Kanneganti, 2021). Mature DCs display tumor-specific antigens to activate cytotoxic T lymphocytes, which then eliminate tumors (Wang et al., 2013).

Targeted drugs have also been discovered that selectively trigger pyroptosis in tumor cells (Table 5). Val-boroPro triggers pyroptosis in primary acute myeloid leukemia (AML) cells by activating the inflammasome sensor protein CARD8 which then activates procaspase-1 (Johnson et al., 2018). In a melanoma study, it was found that the combination of BRAFi and MEKi could potentially have an antitumor effect by inducing pyroptosis through GSDME (Erkes et al., 2020). Additionally, the combination of DDP and BI2536 (a PLK1 kinase inhibitor) was observed to induce pyroptosis in esophageal cancer cells (Wu M. et al., 2019). In a study conducted by Dobrin et al., triple-negative breast cancer cells were exposed to ivermectin, resulting in the activation of the pannexin-1 pathway. This activation led to the overexpression of P2X4/P2X7 receptors, the release of ATP and ultimately the induction of pyroptosis (Draganov et al., 2015). Several drugs, including metformin, anthocyanin, and DHA have been found to trigger GSDMD mediated pyroptosis in different types of cancers (Pizato et al., 2018; Wang L. et al., 2019; Yue et al., 2019).

## 1.5 Clinical development targeting ferroptosis for cancer treatment

Ferroptosis is a recently discovered RCD pathway distinguished by oxidative and non-apoptotic mechanisms. It is characterized by iron-dependent lipid peroxide damage in mitochondria and a lack of glutathione peroxidase 4 (GPX4) and is distinct from apoptosis, autophagy, and necrosis (Dixon et al., 2012) (Figures 1, 2). From a morphological perspective, the cell membrane stays intact while developing blisters. The mitochondria decrease in size, and their membrane density increases. The mitochondrial cristae may either reduce in number or vanish entirely. The nucleus retains its typical size, while the chromatin remains uncondensed. Ferroptosis takes place when there is a disruption in the regulatory system, resulting in the buildup of lipid peroxide to a critical level. Transferrin (TF) attaches to extracellular Fe<sup>3+</sup> and aids in its transport into cells through transferrin receptor 1 (TfR1), where it is subsequently transformed into Fe<sup>2+</sup> (Masaldan et al., 2018). Subsequently, intracellular divalent metal transporter 1 (DMT1) and zinc transporter 8/14 (ZIP8/14) facilitate the storage of Fe<sup>2+</sup> in the intracellular labile iron pool (LIP) (Sterling et al., 2017). Fe<sup>2+</sup> can transfer electrons via the Fenton reaction with peroxide, leading to the generation of oxidizing free radicals. After an excessive buildup of iron within cells, many free radicals engage with polyunsaturated fatty acids (PUFA) present in the phospholipids of cell membranes, leading to the creation of lipid peroxides, which ultimately result in cell death (Doll et al., 2017). The intracellular antioxidant stress system relies on GPX4 to remove excess lipid peroxides. The Cystine/glutamate antiporter (system xc<sup>-</sup>) enables the transfer of glutamate from inside cells to the exterior, while concurrently bringing cystine from outside into the cells. Inhibiting cystine with system xc<sup>-</sup> blockers like erastin reduces

the necessary cysteine levels for GSH production and disrupts GSH synthesis. GPX4 facilitates the hydrolysis of lipid peroxide through the action of GSH. Enhancing ferroptosis requires the inhibition of system Xc<sup>-</sup>, depletion of GSH, and deactivation of GPX4 (Yang et al., 2014).

Cancer cells' higher iron (Fe) accumulation makes them more susceptible to ferroptotic cell death, thereby impacting tumor development, proliferation and metastasis (Table 1) (Maru et al., 2022; Lei et al., 2024; Zhou Q. et al., 2024). Several ferroptosis inducers have been developed, and their effectiveness varies in different cancer types (listed in Table 6) (Luo et al., 2024; Zhou Q. et al., 2024). Sorafenib, an FDA-approved chemotherapeutic for hepatocellular carcinoma (HCC), renal cell carcinoma (RCC), and thyroid cancer stimulates ferroptosis by inhibiting system Xc<sup>-</sup> and glutathione (GSH) formation (Dixon et al., 2014; Sun et al., 2017). Combining sorafenib with sulfasalazine can further inhibit sulfur-based amino acid metabolism, triggering ferroptosis in HCC cells both *in vitro* and *in vivo* (Wang K. et al., 2021). In NSCLC and colon cancer, cisplatin induces ferroptosis by depleting GSH and inactivating GPX4 (Guo et al., 2018). Etoposide, a phenolic anticancer drug, depletes GSH in myeloperoxidase-rich myelogenous leukemia cells, reducing GPX4 and triggering ferroptosis (Kagan et al., 2017). Further, Ma et al. demonstrated that the combination of the lysosome disruptor siramesine with the tyrosine kinase inhibitor lapatinib resulted in the ferroptotic death of breast cancer cells. This was achieved by blocking iron transport and inducing lipid peroxidation (Ma S. et al., 2016). The combination of DHA with cisplatin triggered cell death in pancreatic ductal adenocarcinoma (PDAC) by promoting the degradation of GPX4, creation of ROS and the degradation of ferritin, leading to induction of ferroptosis (Du J. et al., 2021).

Nanotechnology enhances RCD induction by delivering inducers directly to tumors (Mohammadinejad et al., 2019). FePt@MoS<sub>2</sub> nanoparticles, for example, release Fe(II) in the tumor microenvironment, accelerating the Fenton reaction and triggering ferroptosis in various cancer cell lines (Zhang D. et al., 2019). Similarly, additional research showed that zero-valent iron nanoparticles transformed Fe(II) to enhance the Fenton reaction, resulting in mitochondrial lipid peroxidation in oral cancer cells (Huang K. J. et al., 2019). In addition, FSSN based on the metal-polyphenol coordination of Fe(III) and shikonin, led to necroptosis and a reduced GSH level induced ferroptosis in mouse breast cancer cell lines (Feng et al., 2022).

Radiation therapy induces ferroptotic cell death by generating reactive oxygen species (ROS), leading to lipid peroxidation (Lang et al., 2019; Lei et al., 2020; Ye et al., 2020). ROS extract electrons from polyunsaturated fatty acids (PUFAs), forming lipid peroxyl radicals and hydroperoxides. Radiation also upregulates ACSL4 to facilitate PUFA-phospholipid production and also reduces GSH levels, impairing GPX4 and promoting ferroptosis (Lei et al., 2020; Ye et al., 2020; Zhang C. et al., 2022). Moreover, studies have demonstrated that disulfiram induces lysosomal membrane permeabilization through a process dependent on reactive oxygen species (ROS), leading to ferroptosis induction and enhancing the vulnerability of cells to radiation (Ye L. et al., 2021).

ICIs have advanced cancer therapy, but their efficacy is limited without tumor-associated antigens (Ding et al., 2022; Kou et al., 2023). CD8<sup>+</sup> T lymphocytes can suppress tumors by triggering

TABLE 6 Ferroptosis targeting drugs for cancer therapy.

Drug/Compound	Mechanism of action	Cancer type	Clinical status	References
Erastin	Inhibits system Xc <sup>-</sup> depleting GSH	Various Cancers	Preclinical	<a href="#">Bakar-Ates and Ozkan (2024)</a> , <a href="#">Sinha et al. (2024)</a> , <a href="#">Wu et al. (2024a)</a>
RSL3	Directly inhibits GPX4, leading to lipid peroxidation	Various Cancers (Research tool)	Preclinical	<a href="#">Dixon et al. (2014)</a> , <a href="#">Sun et al. (2017)</a>
Sorafenib	Inhibits system Xc <sup>-</sup> ; multi-kinase inhibitor	Hepatocellular Carcinoma, Renal Cell Carcinoma	FDA Approved for HCC, RCC; Investigational for ferroptosis	<a href="#">Dixon et al. (2014)</a> , <a href="#">Sun et al. (2017)</a>
Sulfasalazine	Inhibits system Xc <sup>-</sup> , depleting GSH and inducing ferroptosis	Glioma, Breast Cancer, Hepatocellular carcinoma	FDA Approved for RA and UC; Investigational in cancer	<a href="#">Wang et al. (2021b)</a>
Artesunate	Iron-dependent ROS generator	Pancreatic Cancer, Breast Cancer, lung cancer	FDA Approved for Malaria; Investigational in cancer	<a href="#">(Eling et al., 2015, Wang et al., 2021b, Wang et al., 2024a)</a>
Dihydroartemisinin	GPX4 inhibitor	pancreatic ductal adenocarcinoma	Preclinical studies	<a href="#">Du et al. (2021a)</a>
Lycorine	GPX4 inhibitor	Renal cell carcinoma	Preclinical studies	<a href="#">Du et al. (2021b)</a>
Osimertinib	EGFR inhibitor	Non-small cell lung cancer (NSCLC)	FDA-approved	<a href="#">Zhang et al. (2023)</a>
Lapatinib	inhibits system Xc <sup>-</sup> and HER2/EGFR pathways	Breast Cancer	FDA Approved for HER2+ Breast Cancer	<a href="#">Ma et al. (2016b)</a>
Altretamine	Induces lipid peroxidation leading to ferroptosis	Ovarian Cancer, Head and neck cancer	FDA Approved; Investigational for ferroptosis	<a href="#">Keldsen et al. (2003)</a> , <a href="#">Roh et al. (2016)</a>
FIN56	Promotes degradation of GPX4 and depletes coenzyme Q10	Bladder cancer	Preclinical	<a href="#">Shimada et al. (2016)</a>
FINO2	Oxidizes iron and directly oxidizes lipids, inducing ferroptosis	Various Cancers	Preclinical	<a href="#">Gaschler et al. (2018)</a>
Dihydroartemisinin (DHA)	ROS generation and iron metabolism alteration	Hepatocellular Carcinoma, Leukemia	Preclinical/Clinical Trials	<a href="#">Yuan et al. (2020)</a> , <a href="#">Du et al. (2021a)</a> , <a href="#">Li et al. (2024b)</a>
Carboplatin	Enhances ferroptosis via iron accumulation and ROS generation	Ovarian Cancer	FDA Approved Chemotherapy Agent	<a href="#">Basuli et al. (2017)</a>
Cisplatin	under certain conditions promotes lipid peroxidation	Lung Cancer, Ovarian Cancer	FDA Approved Chemotherapy Agent	<a href="#">Guo et al. (2018)</a>
Etoposide	Depletes GSH	leukemia	Preclinical	<a href="#">Kagan et al. (2017)</a>
Imidazole Ketone Erastin (IKE)	More potent analog of erastin; inhibits system Xc <sup>-</sup>	Various Cancers	Preclinical	<a href="#">Zhang et al. (2019c)</a>
ML162 and ML210	Potent GPX4 inhibitors	Various Cancers	Preclinical	<a href="#">Viswanathan et al. (2017)</a>
Statins (e.g., Simvastatin)	Decrease coenzyme Q10 synthesis	Prostate Cancer, Breast Cancer	FDA Approved for Hypercholesterolemia; Investigational in cancer	<a href="#">Shimada et al. (2016)</a> , <a href="#">Yao et al. (2021)</a>
SRS16-86	GPX4 inhibitor	Pancreatic Cancer	Preclinical	<a href="#">Pu et al. (2022)</a>
Siramesine	Lysosomal disruptor that induces ferroptosis in combination with lapatinib	Breast Cancer	Preclinical	<a href="#">Ma et al. (2016b)</a>
Vitamin C (High Dose)	Induces ferroptosis via depletion of GSH and iron-dependent ROS generation	Colorectal Cancer, Pancreatic Cancer	Clinical Trials	<a href="#">Yun et al. (2015)</a> , <a href="#">Wang et al. (2021d)</a>
β-Elementene	Induces ferroptosis through regulation of iron metabolism	Glioblastoma, Lung Cancer	Preclinical	<a href="#">Tan et al. (2021)</a>
FePt@MoS2	release Fe(II) in the TME, accelerating the Fenton reaction	Solid tumors	Preclinical	<a href="#">Zhang et al. (2019b)</a>

(Continued on following page)



TABLE 6 (Continued) Ferroptosis targeting drugs for cancer therapy.

Drug/Compound	Mechanism of action	Cancer type	Clinical status	References
Zero-valent iron nanoparticles transformed Fe(II)	to enhance the Fenton reaction	Oral cancer cells	Preclinical	Huang et al. (2019a)
FSSN	Reduces GSH levels	Breast cancer	Preclinical	Feng et al. (2022)

necroptosis, pyroptosis, and ferroptosis (Tang et al., 2020; Chen L. et al., 2021; Liao P. et al., 2022; Wang Z. et al., 2022). Unique RCDs in the TME stimulate proinflammatory cytokines and cytotoxic T cell infiltration, enhancing ICI responsiveness (Workenhe et al., 2020). Lipid peroxides generated during ferroptosis signal DCs to present tumor antigens to CD8<sup>+</sup> T cells, improving immunotherapy (Zhao et al., 2022). Combining ferroptosis inducers with ICIs may enhance cancer cell susceptibility to immunotherapy. Wang and colleagues have demonstrated that the concurrent administration of a GPX4 inhibitor, cyst(e)inase, and PD-L1 inhibition enhances T cell-mediated antitumor immune responses and synergistically promotes ferroptotic death of cancer cells (Wang W. et al., 2019). On the other hand, ferroptosis inhibition therapy yielded greater antitumor efficacy when used in combination with anti-PD-1 antibodies [346].

However, ferroptosis can sometimes promote tumor initiation and progression (Dang et al., 2022). Ferroptosis-induced inflammation may drive necroinflammation-associated malignancies, and immune cell susceptibility to ferroptosis can undermine tumor suppression or promote tumor development (Bell et al., 2024). Ferroptotic cancer cells may also have immunosuppressive effects that enhance tumor growth (Chen X. et al., 2021; Qi and Peng, 2023). In addition, the ferroptosis of non-tumor cells is linked to a diminished ability to combat tumors due to a decrease in the generation of cytotoxic cytokines. Utilizing the ferroptosis inhibitor ferrostatin-1 effectively prevents CD8<sup>+</sup> T cell ferroptosis by inhibiting lipid peroxidation (Wang W. et al., 2019). As a result, the production of pro-inflammatory cytokines is enhanced, leading to the elimination of tumors. Ferroptosis inhibition yields enhanced antitumor effectiveness when combined with anti-PD-1 antibodies (Ma et al., 2021). Further, Inhibiting ferroptosis could mitigate adverse effects from therapies promoting it, suggesting its suppression might be a viable cancer treatment strategy in certain contexts.

Currently, a phase II clinical study is assessing the ferroptosis inhibitor MIT-001 for preventing oral mucositis in lymphoma or multiple myeloma patients undergoing conditioning chemotherapy with autologous hematopoietic stem cell transplantation (NCT05493800).

## 1.6 New roles for cuproptosis in cancer cell death and targeting strategies

In 2019, Tsvetkov et al. discovered Cu-dependent death while investigating the anticancer mechanism of the Cu ionophore elesclomol (Tsvetkov et al., 2019). It was discovered that administering elesclomol to a mouse model of multiple myeloma decreased the cancer cells' resistance to the damage caused by

proteasome inhibitors. Mechanistically, reduced Cu(I) is produced when elesclomol-bound Cu(II) interacts with the mitochondrial enzyme ferredoxin 1 (FDX1), raising ROS levels (Nagai et al., 2012; Tsvetkov et al., 2019). Lipid peroxidation was once thought to be the cause of elesclomol's lethality (Gao et al., 2021). Later, in 2022, they reported that intracellular copper build-up causes mitochondrial lipoylated protein oligomerization and destabilizes Fe-S cluster proteins, resulting in cuproptosis, an independent mode of cell death that is different from other RCD pathways (Ge et al., 2022). Research in the domains of cancer pathology and cell physiology has long focused on the role of copper in tumor progression, with studies emphasizing the critical connection between cuproptosis and cancer. Tumor angiogenesis and metastasis are activated by copper, a proangiogenic factor (Xu et al., 2022). Dysfunctional copper metabolism is the cause of both radioresistance and chemoresistance (Liu et al., 2022; Yang et al., 2022). Increased serum copper levels have been linked in a number of studies to disease invasion and tumor stage in patients with breast, lung, and colorectal cancer (Baszuk et al., 2021; Cui et al., 2021; Tsang et al., 2022). On the other hand, cuproptosis causes endothelial cell dysfunction, oxidative stress, and mitochondrial damage in malignant cells by interfering with lipid metabolism (Halliwell and Chirico, 1993; Ruiz et al., 2021).

Further, elevated Cu has been strongly associated with the increased expression level of hypoxia-inducible factor 1 $\alpha$  (Feng et al., 2009; Wu Z. et al., 2019), inducing angiogenesis, and neovascularization leading to increased production of vascular endothelial growth factor (Zimna and Kurpisz, 2015). Elevated expression of intracellular Cu-dependent protein MEMO1, an oncogenic protein, has been associated with migration and invasion of breast and lung cancer cells (MacDonald et al., 2014). Zhang et al. have demonstrated that MEMO1 preferentially binds to Cu(I) and not Cu(II) and thus protects cells from redox activity (Zhang et al., 2022d). Consequently, releasing Cu ions and preventing the spread of tumor cells may be achieved by devising a suitable strategy to disrupt the Cu(I) binding site on the MEMO1 protein.

Cuproptosis may prevent the spread of cancer cells and reduce their proliferation (Li J. et al., 2022; Feng et al., 2024). Cuproptotic tumors exhibit reduced angiogenesis and respond well to therapy with sunitinib and sorafenib (Li K. et al., 2022). Cancer cells have developed mechanisms to defend against Cu-induced apoptosis (Table 1). For example, individuals with hepatocellular carcinoma (HCC) had significantly reduced levels of the critical cuproptosis regulator FDX1, making HCC cells resistant to cuproptosis (Zhang Z. et al., 2022). More advanced tumor-node-metastasis stages are closely linked to reduced FDX1 expression. Additionally, shorter survival rates have been associated with decreased FDX1 expression across various cancer types (Wang T. et al., 2022).

TABLE 7 Cuproptosis targeting drugs for cancer therapy.

Drug/Treatment	Target/Pathway	Cancer Type(s)	Clinical status	References
Elesclomol (ES)	Acts as a copper ionophore, increasing intracellular copper levels	Melanoma, Lung Cancer, Lymphoma	Phase III trial (for melanoma) in combination with chemotherapy for advanced melanoma.	O'Day et al. (2013), Tsvetkov et al. (2022)
Disulfiram (DFS)	Forms a complex with copper, inducing proteasome inhibition	Breast Cancer, Prostate Cancer, Glioblastoma	Phase I clinical trial	Kelley et al. (2021)
Tetrathiomolybdate (TM)	Copper chelator that depletes systemic copper,	Breast Cancer, Kidney cancer	Phase II clinical trial	Brewer et al. (2000), Redman et al. (2003), Chan et al. (2017)
D-Penicillamine	Chelates copper, reducing intracellular levels	Lung cancer, Breast cancer	Preclinical	Sciegienka et al. (2017)
Trientine	Copper chelator reducing systemic copper levels	Various Cancers	Preclinical/Clinical Trials	Yoshii et al. (2001), Huang et al. (2019b)
Copper-64 Radiopharmaceuticals	Utilize radioactive copper isotopes for imaging and targeted radiotherapy, affecting cuproptosis pathways	Neuroendocrine Tumors, Prostate Cancer	Clinical Trial	Boschi et al. (2018), Zhou et al. (2019)
Copper Oxide Nanoparticles	Increase intracellular copper levels, inducing oxidative stress	Breast.colotectalr yhrng Colon cancer	Preclinical	Benguigui et al. (2019), Ghasemi et al. (2023), Abdollahzadeh et al. (2024)
Ammonium Tetrathiomolybdate	Copper chelator that reduces angiogenesis and metastasis	Breast Cancer, Lung Cancer	Phase I/II Clinical Trials	Chisholm et al. (2016)

Copper ionophores, or cuproptosis-related drugs which trigger cuproptosis, may hold promise for future tumor treatments (Table 7) (Springer et al., 2024; Wang Y. et al., 2024). Elesclomol (ES) and Disulfiram (DFS) induce apoptosis by transporting copper ions into cells and mitochondria, resulting in the oligomerization of dihydrolipoamide *s*-acetyltransferase, decreased stability of Fe-S clusters and interaction with Npl4 (Reeder et al., 2011). Copper complexes with bis(thiosemicarbazone) ligands raise copper ion levels in both cancer cells and in Chlamydia-infected host cells (Cater et al., 2013; Marsh et al., 2017). Furthermore, derivatives of quinolines also function as copper ionophores (Oliveri et al., 2017; Oliveri, 2022). Derivatives from simple compounds such as 3-Hydroxyflavone (Dai et al., 2017), as well as more intricate copper ionophores like Hydrophilic Temperature-Sensitive Liposomes (Gaal et al., 2020) and a copper ionophore designed using salicylaldehyde isonicotinoyl hydrazone (Ji et al., 2018), also increase copper levels inside cells.

Among these agents, Elesclomol (ES) and Disulfiram (DFS) are currently undergoing evaluation in clinical trials (Xie J. et al., 2023). Recent trials investigating ES (O'Day et al., 2013) and DFS (Kelley et al., 2021) have demonstrated excellent safety profiles. Current research in this area is focused on nanomedicines that combine copper ions with copper ionophores (Lee et al., 2023; Zhou et al., 2023). Combining other cancer treatments with cuproptosis-related therapy may yield improved outcomes. Overall, copper ionophores may have greater efficacy in tumors with elevated mitochondrial metabolism. In the phase III clinical trial of ES, the impact of ES varied among individuals with low serum LDH levels (O'Day et al., 2013). Thus, serum LDH levels may serve as a prognostic indicator in the future clinical use of cuproptosis-related medications, helping to assess the potential effectiveness of these drugs. To summarize, copper ionophores can be combined with targeted therapeutic agents like TKI and PI. This combination is most effective in tumors with high mitochondrial metabolic status. Additionally,

LDH can be used as a predictor to guide treatment before drug administration and as a prognostic indicator afterward. Further research is necessary to ascertain the feasibility of cuproptosis-inducing therapies in select patients with distinct types of cancer.

## 1.7 Parthanatos as target in cancer treatment

Parthanatos is a cell death mechanism controlled by PARP-1 and is distinct from apoptosis and necroptosis (Harraz et al., 2008) (Figures 1, 2). In parthanatos, abnormal PARP-1 activation causes excessive PAR production (Dawson and Dawson, 2004), mitochondrial membrane depolarization decreases ATP and NADPH levels, and triggers AIF translocation from mitochondria to the nucleus. Additionally, AIF binds to MIF nuclease, activating it (Wang Y. et al., 2019). After translocating to the nucleus, AIF and MIF cause nuclear shrinkage, chromatin agglutination, and big DNA fragments (15–50 KB) that cause parthanatos (Zhou et al., 2021). The lack of caspase is its main characteristic.

There is a strong correlation between parthanatos and tumor formation and progression (Zhou et al., 2021). The expression level of PARP-1 in breast cancer, ovarian cancer, endometrial cancer, lung cancer, skin cancer and non-Hodgkin's lymphoma is elevated compared to normal tissues, thus establishing a strong association between parthanatos and these cancers (Harraz et al., 2008; Fong et al., 2009; Galia et al., 2012; Dorsam et al., 2018; Pazzaglia and Pioli, 2019). PARP-1 knockout mice showed a considerable decrease in susceptibility to epithelial malignancies. Downregulating PARP-1 protein hinders the action of NF- $\kappa$ B and the expression of tumor-promoting proteins controlled by NF- $\kappa$ B, thereby preventing the induction of parthanatos (Pazzaglia and Pioli, 2019). Additionally, the absence of PARP-1 in mice resulted in a notable decrease in the occurrence of colorectal cancer caused by oxymethane (AOM) and dextran sulfate sodium (DSS). Reducing PARP-1 protein levels may

TABLE 8 Parthanatos targeting drugs for cancer therapy.

Drug/Treatment	Target/Pathway	Cancer Type(s)	Clinical status	References
Olaparib (Lynparza)	PARP inhibitor; inhibits PARP-1/2 leading to DNA damage accumulation	BRCA-mutated Ovarian Cancer, Breast Cancer pancreatic cancer, and prostate cancer	FDA approved	Clarke et al. (2024), Fenton and Hussain (2024), Kawamoto et al. (2024), Lee et al. (2024), Shah et al. (2024)
Rucaparib (Rubraca)	PARP inhibitor	BRCA-mutated Ovarian Cancer, Prostate Cancer	FDA approved	Monk et al. (2022), Sayyid et al. (2024)
Niraparib (Zejula)	PARP inhibitor inducing parthanatos via DNA damage accumulation	Ovarian Cancer	FDA approved	Wu et al. (2024b)
Veliparib (ABT-888)	PARP inhibitor inducing parthanatos; used in combination therapies	Various Cancers	Phase II/III Clinical Trials	Mizuno et al. (2023), Rodler et al. (2023), Zhao et al. (2023), Dieras et al. (2024), Kashbour et al. (2024), Sun and Li (2024)
Talazoparib (Talzenna)	PARP inhibitor with strong PARP-trapping ability	BRCA-mutated Breast Cancer, prostate cancer	FDA approved	Fizazi et al. (2024), Heiss et al. (2024), Narang et al. (2024), Piha-Paul et al. (2024), Telli et al. (2024)
$\beta$ -Lapachone	PARP inducer	Hepatocellular carcinoma	preclinical	Zhao et al. (2021a)
Deoxy podophyllotoxin (DPT)	PARP inducer	Glioma	preclinical	Ma et al. (2016a)
PJ34	PARP inhibitor	Various Cancers	Preclinical	Shi et al. (2014b)
CEP-8983	PARP inhibitor	leukemia	Preclinical	Dilley et al. (2014)
E7016 (GPI 21016)	PARP inhibitor	Solid Tumors	Phase I Clinical Trials	Russo et al. (2009)
INO-1001	PARP inhibitor	Melanoma, Glioblastoma	Preclinical	Mason et al. (2008)

effectively prevent induced colorectal cancer by suppressing the expression of cyclin D and STAT3 (Dorsam et al., 2018).

The impact of parthanatos on carcinogenesis and tumor development manifests in two key dimensions (Zhou et al., 2021). During rapid cellular proliferation, DNA is highly susceptible to radiotherapy or chemotherapy, leading to tumor cell death. PARP-1 plays a crucial role in DNA repair and is essential for tumor cell survival. Hence, inducing apoptosis in tumor cells can be achieved by suppressing PARP-1 activity. Conversely, the occurrence of parthanatos primarily arises from the abnormal activation of PARP-1. Promoting parthanatos in tumor cells by augmenting PARP-1 activity can impede tumor cell proliferation. Given PARP-1's involvement in several DNA repair pathways and its role in maintaining genomic stability (Yang et al., 2020), modulating PARP-1 activity may be therapeutic for treating associated malignancies (Table 8).

In clinical trials, PARP inhibitors are mostly administered to cancer patients with homologous recombination repair deficiencies including those with breast and ovarian cancers carrying BRCA1 and BRCA2 mutations (gBRCA1/2m) and castration-resistant prostate cancer. Currently, Olaparib (Clarke et al., 2024; Fenton and Hussain, 2024; Kawamoto et al., 2024; Lee et al., 2024; Shah et al., 2024), niraparib (Wu X. et al., 2024), rucaparib (Monk et al., 2022; Sayyid et al., 2024), veliparib (Mizuno et al., 2023; Rodler et al., 2023; Zhao et al., 2023; Dieras et al., 2024; Kashbour et al., 2024; Sun and Li, 2024) and talazoparib (Fizazi et al., 2024; Heiss et al., 2024; Narang et al., 2024; Piha-Paul et al., 2024; Telli et al., 2024) hinder the cancer-fighting effects of parthanatos by suppressing the catalytic function of PARP-1 and PARP-2 (Fong

et al., 2009; Sandhu et al., 2013; Mateo et al., 2016; de Bono et al., 2017; Nishikawa et al., 2017; Wu X. et al., 2024).

$\beta$ -Lapachone, a naturally occurring compound derived from the bark of the lapacho tree, triggers parthanatos by activating the NQO1-dependent ROS-mediated RIPK1-PARP1-AIF pathway, leading to the death of hepatocellular carcinoma cells (Zhao W. et al., 2021). This process was prevented by the inclusion of a PARP-1-specific inhibitor (Park et al., 2014). Deoxy podophyllotoxin (DPT), a naturally occurring chemical derived from *Anthriscus sylvestris*, effectively suppressed glioma growth by promoting the generation of excessive reactive oxygen species (ROS), enhancing PARP-1 expression and facilitating AIF translocation to the cell nucleus. This has been shown in both xenograft glioma models and in glioma cells cultured *in vitro* (Ma D. et al., 2016).

## 2 Conclusion and future perspective

The evolution of cancer therapy always involves trial and error, but discovery of novel mechanisms to target the mission-critical events shared by all tumors offers a glimpse of previously unthinkable therapeutic possibilities (Debela et al., 2021; Levantini, 2023). Understanding carcinogenesis, especially through the identification of altered cellular processes that maintain cancer cells and the development of diagnostic and prognostic biomarkers, has been made possible by studying these altered cell death pathways (Koren and Fuchs, 2021; Peng et al., 2022; Zhou Y. et al., 2024). Since RCD pathways are fundamental to the genesis of all tumors, they present clear targets for therapeutic

intervention in all cancer types (Koren and Fuchs, 2021; Peng et al., 2022; Gong et al., 2023). Moreover, detecting abnormalities in these signaling pathways can aid in identifying the DNA, mRNA and protein mutations present in cancer cells, and may play a significant role in determining the efficacy of specific targeted therapies (Waarts et al., 2022; Chitluri and Emerson, 2024; Liu B. et al., 2024). While a tumor's mutational profile may impact a therapy's effectiveness, identifying altered RCD pathways may yield identification of novel targets.

The complexity of the cellular signaling that occurs in tumor cells presents the biggest obstacle to addressing the dysregulated pathways in distinct cancers (Bou Antoun and Chioni, 2023; Swanton et al., 2024). Crosstalk and inhibitory feedback mechanisms are just two examples of the many elements that obstruct targeted signaling pathways. Additionally, the risk of resistance selection exists with all tumor therapies and this risk may be exacerbated by the genetic plasticity present in most malignancies (Emran et al., 2022; Khan et al., 2024).

The primary therapeutic challenge in targeting RCD pathways for cancer treatment lies in the emergence of resistance mechanisms (D'Amico and De Amicis, 2024). Cancer cells often experience genetic and epigenetic changes that enable them to evade or inhibit cell death signals, even in the presence of targeted therapies designed to activate these pathways (Ozyerli-Goknar and Bagci-Onder, 2021; Tufail et al., 2024). For instance, the overexpression of anti-apoptotic proteins like BCL-2 and BCL-XL or mutations in tumor suppressors such as TP53 can inhibit apoptosis, allowing cancer cells to escape death induced by chemotherapy (Mohammad et al., 2015). In a similar vein, autophagy—a mechanism that enables cells to survive under stress—can be exploited by cancer cells to endure therapeutic damage, resulting in certain cancers, such as pancreatic and lung cancer, becoming resistant to drugs aimed at metabolic pathways (Li et al., 2019; Mele et al., 2020).

Ferroptosis, serves as another significant instance where resistance develops (Nie et al., 2022). The overexpression of GPX4, a lipid peroxidase enzyme, diminishes oxidative stress and inhibits ferroptosis-mediated cell death (Xie Y. et al., 2023), enabling cells to escape therapies aimed at triggering this type of RCD, particularly in liver and pancreatic cancers. Resistance to necroptosis, arises from the inactivation of essential regulators such as RIPK1 and RIPK3, resulting in treatment resistance in cancers including glioblastoma (Xie Y. et al., 2023) and colorectal cancer (Feng et al., 2015). In cuproptosis, cancer cells evade copper-induced cell death by disrupting copper ion homeostasis, with changes in proteins such as FDX1 and DLAT contributing to resistance in lung and melanoma cancers (Abdullah et al., 2024).

Moreover, pyroptosis, can be inhibited by the dysregulation of inflammasome components such as NLRP3 and caspase-1 (Zheng M. et al., 2020). This enables cancer cells to evade the inflammatory response typically associated with pyroptosis. This evasion mechanism has been noted in cancers including colorectal, gastric, and breast cancer. Ultimately, parthanatos, associated with the overactivation of PARP1 due to DNA damage, is often evaded in breast and ovarian cancers by the overexpression of PARP1 or mutations in related pathways, which diminishes the effectiveness of PARP inhibitors in these instances (Pazzaglia and Pioli, 2019).

These examples illustrate how cancer cells' capacity to manipulate and resist RCD pathways complicates therapeutic strategies. The

flexibility and redundancy in cell death mechanisms necessitate the creation of combination therapies or innovative strategies to re-sensitize cancer cells, highlighting the importance of addressing these resistance mechanisms across different cancers. Furthermore, recent high-throughput sequencing data demonstrate the significance of these dysregulated signaling pathways in sustaining supportive TMEs that facilitate the growth and metastasis of numerous solid tumors (Wang et al., 2023). Understanding the composition and function of the TME is thus crucial for deciphering the impact of genetic and epigenetic changes that occur in tumors and the cells that surround them. By studying various tumor types, researchers may identify common pathways that contribute to tumor development.

While the caveats associated with targeting RCD pathways for cancer therapies described above are challenging, the most effective approach to address these issues likely requires use of more advanced combination therapies that target multiple lesions unique to tumors simultaneously. Building a pathway interaction network to determine the functional dependencies between different signaling pathways may offer new perspectives on disease causes and lead to development of more effective drug formulations. Future research should place a stronger emphasis on the utilization of combination therapies for studies employing patient-derived xenografts, organoids/tumoroids and genetically modified mouse models to target oncogenic signaling pathways, RCD and the TME.

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