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REVIEW

Therapeutic strategies of targeting non-apoptotic regulated cell death (RCD) with small-molecule compounds in cancer

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Small-molecule compound;
Cancer therapy

Abstract Regulated cell death (RCD) is a controlled form of cell death orchestrated by one or more cascading signaling pathways, making it amenable to pharmacological intervention. RCD subroutines can be categorized as apoptotic or non-apoptotic and play essential roles in maintaining homeostasis, facilitating development, and modulating immunity. Accumulating evidence has recently revealed that RCD evasion is frequently the primary cause of tumor survival. Several non-apoptotic RCD subroutines have garnered attention as promising cancer therapies due to their ability to induce tumor regression and prevent relapse, comparable to apoptosis. Moreover, they offer potential solutions for overcoming the acquired resistance of tumors toward apoptotic drugs. With an increasing understanding of the underlying mechanisms governing these non-apoptotic RCD subroutines, a growing number of small-molecule compounds targeting single or multiple pathways have been discovered, providing novel strategies for current cancer therapy. In this review, we comprehensively summarized the current regulatory mechanisms of the emerging non-apoptotic RCD subroutines, mainly including autophagy-dependent cell death, ferroptosis, cuproptosis, disulfidptosis, necroptosis, pyroptosis, alkaliptosis, oxeiptosis, parthanatos, mitochondrial permeability transition (MPT)-driven necrosis, entotic cell death, NETotic cell death, lysosome-dependent cell death, and immunogenic cell death (ICD). Furthermore, we focused on discussing the pharmacological regulatory mechanisms of related small-molecule compounds. In brief,

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these insightful findings may provide valuable guidance for investigating individual or collaborative targeting approaches towards different RCD subroutines, ultimately driving the discovery of novel small-molecule compounds that target RCD and significantly enhance future cancer therapeutics.

1. Introduction

Regulated cell death (RCD), a manageable cell death mechanism that involves one or more highly organized cascades of signals, can be targeted for pharmacological intervention[1]. It was proposed in 1842 because of the observation that the toad notochord is removed by controllable cell death[2]. In addition to development, RCD subroutines are essential for homeostasis, tissue balance, and immunity, which can be divided into apoptotic and non-apoptotic categories according to the different morphology, molecular mechanisms, and function[3]. Non-apoptotic RCD subroutines generally refer to RCD subroutines other than apoptosis, identified separately for their potential to combat tumor resistance[4,5].

Apoptosis, discovered in 1972, is the earliest form of RCD. It is a programmed physiological process that leads to active and orderly cell death through gene regulation. Apoptosis is essential for tissue cell renewal and can also occur spontaneously in tumors, resulting in tumor regression to some extent[6]. Interestingly, the discovery of apoptosis sparked a flurry of research into RCD; as early as ten years ago, the mechanisms of apoptosis had been revealed as much as possible[7]. Apoptosis mainly consists of an extrinsic pathway and an intrinsic pathway, both of which depend on the regulation of caspase family proteases[8,9]. The death receptor, which receives the death signal and binds to the corresponding death-inducing ligand, triggers the recruitment of death-related proteins to activate caspase-8 and initiates extrinsic apoptosis[10]. The intrinsic pathway of apoptosis is primarily initiated by mitochondrial outer membrane permeabilization and alterations in mitochondrial-related apoptotic proteins due to intrinsic stress factors. This leads to cytochrome c to be released and bind to Apaf-1, recruiting and activating caspase-9, which then activates caspase-3, ultimately inducing intrinsic apoptosis[8]. In addition, in the presence of endoplasmic reticulum (ER) stress, disturbed Ca^{2+} activates calcium-dependent protein kinases to directly cleave and activate caspase-12, leading to ER-mediated apoptosis[11]. With the deepening exploration of apoptosis, the mechanism was gradually revealed and the critical regulators were discovered; in particular, promoting apoptosis has become one of the important strategies for cancer therapy[12].

Several non-apoptotic RCD subroutines have been discovered and are gaining attention as promising cancer therapies due to their effectiveness in inducing tumor regression and preventing relapse, comparable to apoptosis[1]. For instance, autophagy can induce cell death was first proposed by Clarke in 1990, which was subsequently classified as a form of RCD and named autophagy-dependent cell death[13]. In 2000, lysosome-dependent cell death was identified, which is commonly initiated by lysosomal membrane permeabilization (LMP), resulting in the release of lysosomal cathepsin to trigger cell death[14]. Moreover, pyroptosis, a newly discovered cell death starting from the inflammatory system activation, was identified in 2001; the activated NLR family pyrin domain containing 3 (NLRP3) inflammatory system induces caspase proteins to cleave gasdermin family members to trigger cell death[15]. In addition, mitochondrial permeability transition (MPT)-driven necrosis was found in 2003, which is a type of RCD with Ca^{2+} overload, cyclophilin D (CypD) activation, mitochondria permeability transition pore (MPTP) opening, and mitochondrial membrane depolarization[16]. NETotic cell death was discovered in 2004, and it occurs primarily during bacterial infections and is initiated by the increase of neutrophil extracellular traps (NETs)[17]. Then, in 2005, necroptosis was found, a unique mechanism of cell death with morphological characteristics and caspase activity distinct from apoptosis. Necroptosis mainly depended on tumor necrosis factor (TNF) and receptor-interacting serine/threonine kinases 1 and 3 (RIPK1, RIPK3), and the executioner protein mixed lineage kinase domain-like pseudokinase (MLKL), and RIPK1 is often ubiquitinated by cellular inhibitors of apoptosis (cIAP1/2) and linear ubiquitin chain assembly complex (LUBAC) or cylindromatosis (CYLD)[18]. In the same year, immunogenic cell death (ICD) was also discovered, namely, some chemotherapy drugs often induce the release of calreticulin (CRT, also known as CALR), ATP, and high mobility group box protein B1 (HMGB1), enhancing immune response and causing cell death[19]. Moreover, entotic cell death was discovered in 2007, primarily in the form of endogenous phagocytosis and cell-to-cell killing[20]. In the same year, parthanatos, a poly ADP-ribose polymerase-1 (PARP-1) dependent non-apoptotic RCD subroutine, was identified, which is commonly initiated by DNA damage, abnormally activating PARP-1 and inducing apoptosis-inducing factor (AIF) and macrophage migration inhibitor factor (MIF) translocation to nuclear with the accumulation of poly ADP-ribose (PAR) to trigger cell death[21]. In addition, ferroptosis, a novel iron-dependent RCD subroutine was proposed in 2012, which is primarily driven by glutathione depletion and lipid peroxidation[22]. In 2018, alkaliptosis was identified as a novel non-apoptotic RCD subroutine that is initiated by lysosomal pH dysfunction, leading to increased pH to trigger cell death[23]. In the same year, oxeiptosis, a reactive oxygen species (ROS)-dependent RCD subroutine, was first identified, which is mainly mediated by the KEAP1/PGAM5/AIFM1 axis to induce protein oxidation and DNA damage to trigger cell death[24]. Cuproptosis, a recently discovered form of RCD, is primarily triggered by an excess of copper[25]. This finding is significant due to the research advancements in ferroptosis. In 2023, disulfidptosis was discovered as a new form of non-apoptotic RCD. It occurs mainly during glucose starvation when cysteine cannot convert to cystine due to insufficient nicotinamide adenine dinucleotide phosphate (NADPH). This leads to the buildup of disulfide bonds, causing disulfide stress, which activates Rac1-WAVE regulatory complex (WRC)-actin-related protein 2/3 (Arp2/3) to induce actin network collapse and cell death[26] (Fig. 1).

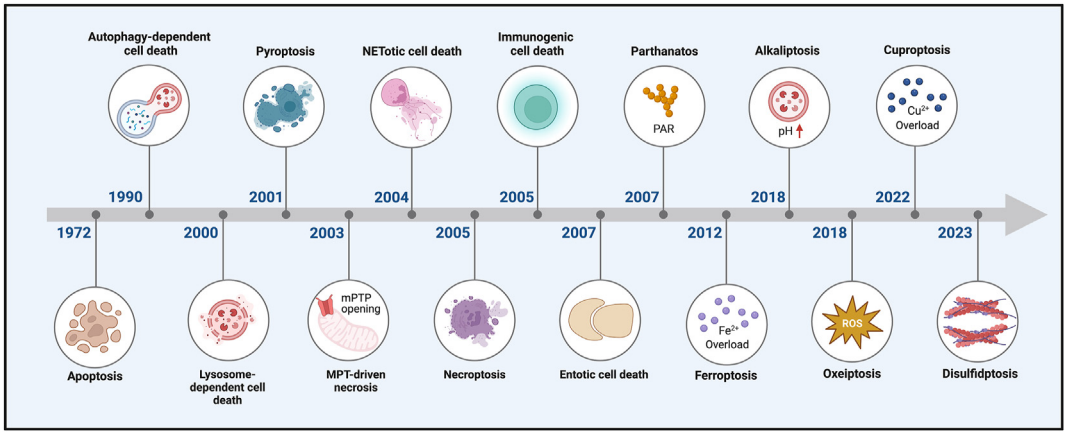

Figure 1 The timeline of different subroutines of RCD. Apoptosis was discovered in 1972, which is the earliest discovered RCD subroutine. Subsequently, several non-apoptotic RCD subroutines have been discovered.

Notably, abnormalities in the RCD process will break homeostasis, and evading RCD is one of the important hallmarks of cancer[27]. Due to the high controllability of RCD, sensible therapeutic interventions to return it to normal can enhance the therapy. Thus, a deeper investigation of various RCD mechanisms will aid in the creation of therapies that accurately manipulate RCD, ultimately leading to an improvement in cancer treatment[1]. Small-molecule compounds targeting apoptosis have been developed for over 30 years, and there are currently U.S. Food and Drug Administration (FDA)-approved anti-tumor drugs (*e.g.*, Trabectedin), but their efficacy is not optimal[28]. The most fundamental explanation is the resistance of treatments targeting apoptosis-related proteins represented by the BCL-2 family[8]. As a result, there is an urgent need to better understand the mechanism of apoptosis resistance while also developing apoptosis replacement therapies to improve cancer treatment. Importantly, targeting non-apoptotic RCD subroutines has also been found to induce tumor regression and prevent recurrence, indicating a viable approach to combating apoptosis resistance[1,3,4]. For instance, autophagy inducer ABTL0812 has excellent antitumor activity in multiple human cancer cells, and its clinical phase 1 study in advanced solid tumors has been completed (NCT02201823) with satisfactory safety and tolerability[29]. Given the existing detailed summary of the apoptosis molecular mechanism and pharmacological regulation in cancer therapy[7,8], as well as the pressing need to combat apoptosis-related drug resistance, in this review, we systematically summarized critical regulatory mechanisms of emerging non-apoptotic RCD subroutines, including autophagy-dependent cell death, ferroptosis, cuproptosis, disulfidptosis, necroptosis, pyroptosis, alkaliptosis, oxeiptosis, parthanatos, MPT-driven necrosis, entotic cell death, NETotic cell death, lysosome-dependent cell death, and ICD, especially focused on core pathways that contribute to cancer therapy. Notably, we also summarized the small-molecule compounds targeting the non-apoptotic RCD subroutines, and discussed crosstalk between subroutines mediated by antitumor compounds and the contribution of crosstalk to the drug effectiveness, aiming to provide more meaningful clues to promote more cancer-therapeutic drug discovery.

2. Targeting non-apoptotic RCD subroutines with small-molecule compounds in cancer

2.1. Targeting autophagy-dependent cell death with small-molecule compounds in cancer

2.1.1. The key signaling pathways of autophagy-dependent cell death

Autophagy refers to the physiological process in which damaged organelles and dysfunctional proteins within cells are degraded through lysosomal action (Fig. 2)[4]. Based on the distinct molecular mechanisms involved, autophagy is classified into three types, namely macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA)[30,31]. Currently, macroautophagy is the most extensively studied and commonly referred to as autophagy[31]. The autophagy process can exhibit selectivity or non-selectivity, contingent upon the nature of the substrates undergoing degradation[5]. It is strictly regulated and involves multiple complex steps such as phagosome induction, extension, formation of autophagosomes, fusion with lysosomes, and degradation of contents[32]. Canonical autophagy is initiated by the UNC-51-like kinase (ULK) complex (Fig. 2A). Under external stimuli, adenine monophosphate activated protein kinase (AMPK) and mechanistic target of Rapamycin (mTOR) respond to upstream autophagy signals (*e.g.*, Ras−Raf-mitogen-activated protein kinase kinase (MEK)-extracellular signal-regulated kinase (ERK), PI3K−Akt) to activate ULK1, then cells generate a phagosome, which is a double-membrane structure formed by the combination of ULK complex and PI3KC3 complex[4]. Recently conducted studies have also shed light on the pivotal role played by ATG (autophagy-related) protein 9A-2A oligomeric complexes in the process of membrane generation during phagosome formation[33]. The extension of phagosomes and the formation of autophagosomes are accomplished through two ubiquitin-like conjugation pathways that are catalyzed by ATG7[4]. One pathway involves the conjugation between ATG5−ATG12 followed by interaction with ATG16L to form a polymeric complex that induces bending enlargement of phagosomal membranes asymmetrically recruited by processed microtubule associated protein 1 light chain 3 (LC3)

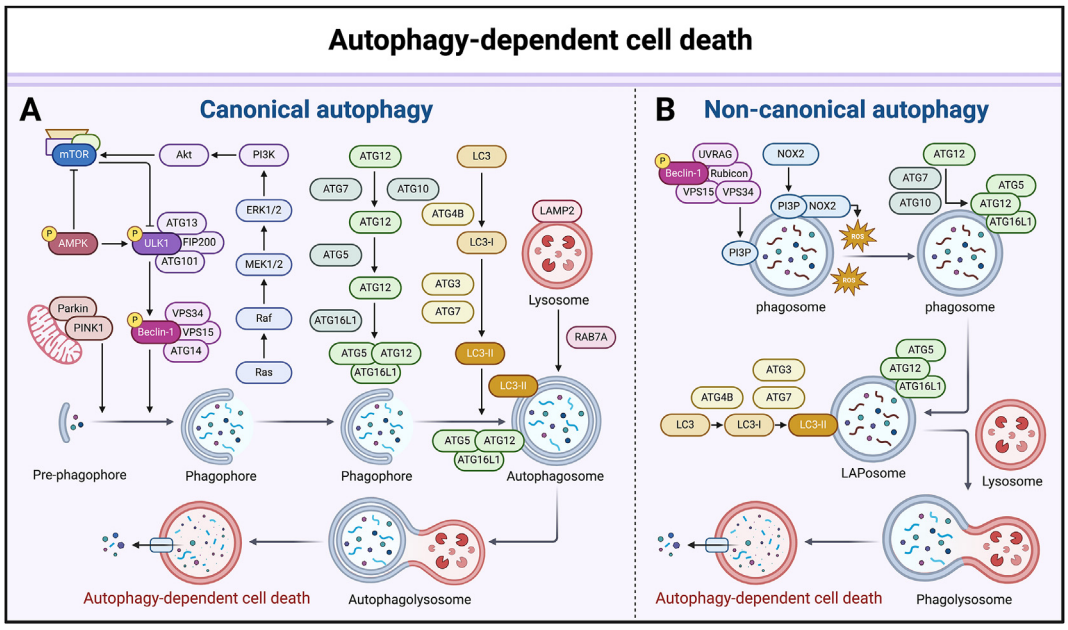

Figure 2 The key signaling pathways of autophagy-dependent cell death. (A) Canonical autophagy is initiated by the ULK complex. AMPK and mTOR respond to upstream autophagy signals (*e.g.*, Ras−Raf−MEK−ERK, PI3K−Akt) to activate ULK1, initiating the autophagy process. The ULK complex activates the PI3K complex to promote phagophore formation. Subsequently, ATG7 and ATG10 promote ATG5, ATG12, and ATG16L1 to form complexes and locate to autophagosome membrane, while ATG4B cleavages LC3, promoting the fusion of autophagosome and lysosome, and finally triggering autophagy-dependent cell death. (B) Non-canonical autophagy is triggered by the PI3KC3 complex, in which the Rubicon mediates VPS34 to produce PI3P on the phagosome membrane and then triggers the combination of NOX2 and PI3P to produce ROS. Subsequently, the downstream ATG5−ATG12−ATG16L1 and ATG7−LC3 are activated, and the single-membraned LAPosome fused with the lysosome to degrade the contents.

at its outer membrane interface with extending membranes[34,35]. The other pathway involves hydrolytic cleavage of LC3 by ATG4, resulting in the generation of LC3-I. Subsequently, LC3-I is activated by ATG7 before being transferred to phosphatidylethanolamine for conjugation with ATG3. This process leads to the production of processed LC3-II, which is recruited onto growing phagosomes and contributes to autophagosome formation[30]. Fusion between autophagic bodies and lysosomes occurs through participation from lysosomal associated membrane protein (LAMP) 2 and GTPase RAB7A[36,37]. The contents enclosed within the autolysosomal vesicles are finally degraded by proteolytic enzymes[38,39]. The distinguishing feature of CMA is its reliance on a unique recognition pentapeptide sequence (KFERQ motif) mediated by the chaperone protein heat shock cognate 71 kDa protein, rather than vesicular structures, to specifically degrade target proteins[40]. The lysosomal membrane receptor protein LAMP2A recognizes and binds to the exposed KFERQ tag, guiding the target protein into lysosomal degradation with high selectivity[41]. In addition, mitochondrial autophagy (mitophagy) is mainly triggered by PTEN-induced kinase 1 (PINK1). When mitochondria are damaged, PINK recruits the E3 ubiquitin ligase Parkin to the mitochondria, inducing mitophagy[42]. In contrast, microautophagy refers to the direct engulfment and degradation of cellular contents by lysosomes or endolysosomes[43]. Research on microautophagy is currently in its early stages compared to macroautophagy and CMA, and its regulatory mechanisms are not well understood[44]. Previous research on the molecular regulation of microautophagy has mainly concentrated on cargo recognition, engulfment, and degradation[43].

Non-canonical autophagy includes LC3-associated phagocytosis (LAP) and LC3-associated endocytosis, which can bypass regulators considered critical in canonical autophagy and even bypass the autophagy promoter ULK complex (Fig. 2B)[45,46]. Consistent with canonical autophagy, the PI3KC3 complex in LAP contains Beclin-1, VPS34, and VPS15; ATG14 is not required in LAP's PI3KC3 complex, but extra UVRAG and Rubicon are[47]. Rubicon mediates VPS34 to produce PI3P on the phagosome membrane and then triggers the combination of NADPH oxidation-2 (NOX2) and PI3P to produce ROS; notably, NOX2 is the critical regulator that distinguishes LAP from canonical autophagy[48]. Subsequently, the downstream ATG5−ATG12−ATG16L1 and ATG7−LC3 are activated; unlike canonical autophagy, the WD repeat domain of ATG16L is necessary to induce LC3 localization on the endolysosomal membrane[49]. Eventually, the single-membraned LAPosome fused with the lysosome to degrade the contents[50]. LC3-associated endocytosis was first discovered in Alzheimer's disease microglia cells, similar to LAP, does not require the ULK complex, but a PI3KC3 complex containing Rubicon is necessary and is currently mainly studied in neurodegenerative diseases[51,52].

Autophagy plays a pivotal role in regulating fundamental metabolic functions, facilitating cells to maintain a dynamic equilibrium between nutrition and energy through decomposition metabolism and recycling mechanisms for the elimination of damaged or harmful components[53,54]. Additionally, it functions as a self-defense system that enables cells to react to difficult situations including starvation, hypoxia, infection, and other harsh conditions. Therefore, autophagy generally has two sides in cancer

therapy. On the one hand, it can supply energy to tumors under harsh conditions, promoting cancer development (also known as cytoprotective autophagy); on the other hand, it can induce tumor death, inhibiting cancer development (also known as autophagy-dependent cell death)[55]. Among them, autophagy-dependent cell death is a non-apoptotic RCD subroutine, which will be discussed in the following section[1].

2.1.2. *Small-molecule compounds targeting autophagy-dependent cell death*

ULK1, a critical regulator in autophagy initiation, is usually combined with FIP200, mATG13, and ATG101 to form complexes to initiate autophagy in mammals[30]. Due to the crucial involvement of ULK1 in autophagy, there has been significant research on compounds that target ULK1. A noteworthy example is LYN-1604, the first developed ULK1 agonist with potential for cancer therapy. LYN-1604 induces autophagy-dependent cell death by activating ULK1 to activate activating transcription factor 3 (ATF3) and Beclin-1/ATG5/LC3 and exerts excellent activation potency with an EC_{50} value of 18.94 nM for ULK1[56]. LYN-1604 demonstrated significant antitumor activity in both MDA-MB-231 human triple-negative breast cancer (TNBC) cells with an IC_{50} of 1.66 μmol/L and MDA-MB-231 cell xenograft model[56].

AMPK is located in the upstream ULK1, which directly phosphorylates to activate the ULK1; meanwhile, AMPK inhibits the classical negative regulator of autophagy mTOR to induce autophagy[57]. Therefore, activation of AMPK is also one of the effective strategies for inducing autophagy-dependent cell death. Fluoxetine, a well-known antidepressant, has been reported to induce autophagy by inhibiting eEF2K and activating the AMPK−mTOR−ULK complex in MDA-MB-231 and MDA-MB-436 cells[58]. Similarly, metformin, a classic diabetes drug, has been reported to activate AMPK to inhibit mTOR, activating ULK1 to induce autophagy-dependent cell death, which exhibits antiproliferative activity with IC_{50} values of 20.2 and 17.9 mmol/L in RPMI8226 and U266 human multiple myeloma (MM) cells, respectively[59]. And, metformin also upregulates Beclin-1 and LC3-II and downregulates p62 to induce autophagy-dependent cell death in 143B and U2OS human osteosarcoma (OS) cells[60]. Moreover, a series of selenocyanate monoamidic acids and diselenide derivatives were synthesized and evaluated for their efficacy against breast cancer (BC) cells; the results have shown that selenocyanate monoamidic acids derivatives **8b** showed reliable antiproliferative activity with IC_{50} values of 21.05, 47.83, 11.89, 59.67, 67.89 and 3.33 μmol/L in PC-3, HTB-54, HT-29, MOLT-4, K562 and MCF-7 cells, respectively; and, diselenide derivatives b showed reliable antiproliferative activity with IC_{50} values of 8.3, 4.91, 11.67, 91.19, 80.89 and 0.00096 μmol/L in PC-3, HTB-54, HT-29, MOLT-4, K562 and MCF-7 cells. Notably, both compounds showed optimal antiproliferative activity in MCF-7 cells; the further mechanism exploration found that **8b** and **10a** activated AMPK and JNK signals, upregulating Beclin-1 and LC3-II while downregulating p62, triggering autophagy-dependent cell death in MCF-7 cells[61]. Fluorinated thiazolidionol has been found to activate AMPK, upregulating LC3 and downregulating p62. This induces autophagy-dependent cell death, resulting in antiproliferative activity in MIA PaCa-2 and PANC-1 human pancreatic adenocarcinoma (PAAD) cells, with IC_{50} values of 8 μmol/L. Additionally, fluorinated thiazolidionol demonstrates a promising anticancer effect *in vivo*, as it regresses tumors in the MIA PaCa-2 xenograft model[62]. Apigenin, present in numerous types of fruits, vegetables, and herbals, has been discovered to stimulate AMPK−ULK1 while inhibiting mTOR, leading to autophagy-dependent cell death in AGS and SNU-638 human gastric cancer (GC) cells[63]. Thioridazine is a common antipsychotic drug that has been reported to activate AMPK and inhibit Wnt/β-catenin, upregulating LC3-II to induce autophagy in glioblastoma (GBM) multiform cells[64]. Moreover, dihydroartemisinin, a natural product extracted from *Artemisia annua*, has also been reported to inhibit Wnt/β-catenin to induce autophagy to reduce the viability of MM cells[65]. Docosahexaenoic acid (DHA) is an essential polyunsaturated fatty acid in the human body, which is more abundant in fish oil; it was reported as early as 2011 for its excellent autophagy regulatory activity, prompting researchers to explore its anticancer activity[66]. In a recent study, it was discovered that DHA can induce autophagy-dependent cell death in MCF-7 cells. This is achieved by upregulating OSGIN1, which stimulates the production of mitochondrial ROS, activating AMPK, and inhibiting mTOR[67]. p53 is a classic tumor suppressor whose frequent mutations in cancer confer carcinogenic effects[68]. Of note, in acute myeloid leukemia (AML), gambogic acid, suberoylanilide hydroxamic acid, and 17-AAG, can trigger autophagy to degrade mutant p53, hence weakening the carcinogenic effect[69]. Moreover, β-asarone, extracted from *Acorus tatarinowii* Schott, has been reported to upregulate p53 to activate AMPK, inhibiting mTOR in U251 cells[70]. Similarly, 6-azauridine has also been reported to activate p53 and AMPK-dependent autophagy to inhibit HCT116 colorectal cancer (CRC) cell proliferation[71]. In addition, naturally occurring *trans*-chalcone, a potential anticancer compound, has also been reported to upregulate p53 and downregulate β-catenin, inducing autophagy-dependent cell death to inhibit HuH7.5 human hepatocellular carcinoma (HCC) cell proliferation[72].

The mTOR is a classical negative regulator of autophagy; as inhibitors are often easier to develop than activators in the field of small-molecule drug discovery, mTOR has become a hot drug target for inducing autophagy-dependent cell death in cancer therapy[73,74]. A group of *N*-(1-benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl) benzamides was found to have activity in PAAD cells. Compound **23** showed the highest activity, with an EC_{50} of 0.62 μmol/L in MIA PaCa-2 cells. Further mechanistic studies revealed that compound **23** inhibited mTORC1, inducing autophagy-dependent cell death to play the role of antiproliferative[75]. Similarly, a natural chalcone cardamonin, identified from a traditional Chinese medicine (TCM) Amomi Fructus Rotundus, has been reported to inhibit mTORC1 to induce autophagy-dependent cell death and exhibit antiproliferative activity with an IC_{50} of 15 μmol/L in SKOV3 human ovarian cancer (OV) cells[76]. Moreover, mTOR inhibitor vistusertib (AZD2014) has been reported to exert antiproliferative activity both *in vitro* and *in vivo* and improve the sensitivity of 8505C human ATC cells to paclitaxel[77]. In addition, a series of fluorescent derivatives have been synthesized and evaluated for activity against A549 human non-small cell lung cancer (NSCLC) cells; among them, compound **8** exhibited optimal antiproliferative activity *via* inhibiting mTOR to induce autophagy[78]. Similarly, a series of fluorescent thiazole-pyrazoline derivatives have been synthesized, and compound **5e** has been found to inhibit mTOR, triggering autophagy and reducing the viability of A549 cells[79]. Additionally, computer-aided drug design has played a vital role in discovering mTOR inhibitors[80,81]. By utilizing techniques such as molecular dynamics simulation, virtual screening, activity testing, and pharmacophore modeling, C-4, an ATP competitive inhibitor of mTOR, has been discovered. Notably, C-4 demonstrated time- and dose-dependent inhibition of proliferation in A549 cells and induced autophagy-dependent cell death by inhibiting both mTORC1 and mTORC2, activating ULK1 to upregulate Beclin-1

and LC3-II while downregulating p62[80]. Similarly, based on pharmacophore modeling, the lead compound, 3-bromo-*N*′-(4-hydroxybenzylidene)-4-methylbenzohydrazide was discovered. After a series of structural modifications, compound **7c** showed strong inhibitory activity against mTOR with an IC_{50} of 0.304 μmol/L; and **7c** also exerted optimal inhibition of proliferation with IC_{50} values of 3.38 ± 1.01 and 4.30 ± 1.82 μmol/L in MDA-MB-231 and MDA-MB-436 cells, respectively. In addition, subsequent investigation revealed that **7c** induces autophagy-dependent cell death through the inhibition of mTOR, upregulating Beclin-1 and LC3-II, and downregulating p62[81].

Moreover, polyphyllin VI (PPVI), is an active ingredient extracted from the herbal medicine *Trillium tschonoskii* Maxim., which has been reported to produce ROS to inhibit mTOR signaling, inducing autophagy-dependent cell death in A549 and H1299 human NSCLC cells[82]. Of note, mTOR is a significant component of PI3K−Akt−mTOR and often responds to the PI3K−Akt signal[83]. For instance, ABTL0812 has been reported to interfere with DEGS1 activity to increase long-chain dihydroceramides, abnormal activating ER stress response and ATF4−DDIT3−TRIB3, leading to competitive binding of TRIB3 to Akt, inhibiting Akt−mTOR[29,84]. Importantly, ABTL0812 has entered the clinical study due to its excellent antitumor activity in multiple human cancer cells as well as A549 and MIA PaCa-2 cells xenograft models[84]. Similarly, HA-1141 has also been reported to activate ATF4 to induce ER stress response and inhibit mTOR in H358 cells, exerting promising antitumor efficacy *in vitro* and *in vivo*[85]. W922 is a chemically synthesized triazine derivative that inhibits PI3K−Akt−mTOR to upregulate Beclin-1 and promote LC3-I conversion to LC3-II in HCT116 CRC cells[86]. LCC03, a chemically synthesized salicylanilide derivative, inhibits Akt−mTOR and exerts promising antiproliferative activity with IC_{50} values of 0.688 ± 0.061 and 4.48 ± 2.58 μmol/L in C4-2 and PC-3 human castration-resistant prostate cancer (PRAD) cells, respectively[87]. Moreover, according to the critical pharmacophore of classical antitumor drugs sorafenib and gefitinib, a series of quinazolinyl-arylurea derivatives were designed and synthesized to test the activities; among them, compound **7j** showed the optimal antiproliferative activity with an IC_{50} of 3.97 ± 0.23 μmol/L in T24 cells[88]. The further mechanism exploration found that **7j** inhibited PI3K−Akt−mTOR, upregulating the phosphorylation of ULK1 while downregulating p62; and, **7j** also induced ferroptosis by inhibiting glutathione peroxidase 4 (GPX4)[88]. Similarly, a series of thieno [2,3-*d*]pyrimidine derivatives were synthesized to test the inhibition of Akt1; among them, compound **9f** showed the optimal antiproliferative activity with an IC_{50} of 0.076 ± 0.010 μmol/L in Huh-7 cells *via* inhibiting Akt−mTOR[89]. Mito-lonidamine, a modified version that specifically targets mitochondria of the clinical study drug lonidamine (LND), significantly improves the therapeutic efficacy both *in vitro* and *in vivo*, which has been reported to inhibit the Akt−mTOR−p70S6K axis in H2030 and H2030BrM3 cells[90]. Additionally, some natural compounds act as anticancer agents by triggering autophagy-dependent cell death through the PI3K−Akt−mTOR. For instance, berberine, a star molecule that existed in TCM *Coptis chinensis* and *Phellodendron chinense* Schneid., has been reported to inhibit Akt−mTORC1 in acute lymphoblastic leukemia (ALL) cells[91]. Similarly, tanshinone IIA, a natural medicine extracted from TCM *Salvia miltiorrhiza* Bunge, has been reported to exert antiproliferative activity by inhibiting PI3K−Akt−mTOR in MCF-7 cells[92]. And, shikonin, a natural naphthoquinone as the major component of TCM *Lithospermum erythrorhizon*, has been reported to inhibit PI3K−Akt−mTOR in SNU-449 and Hep3B cells, exerting promising antiproliferative activity[93]. Sophflarine A, a natural product extracted from TCM *Sophora flavescens*, has been reported to produce ROS to inhibit the PI3K−Akt−mTOR axis and p62, upregulating LC3-II in A549 and H820 cells, slowing tumor growth in the A549 orthotopic xenograft model[94]. Neoalbaconol, a sesquiterpene afforded by *Albatrellus confluens*, has been identified as a novel 3-phosphoinositide-dependent protein kinase 1 (PDK1) inhibitor, which inhibited Akt to downregulate p62 and upregulate LC3-II and inhibit proliferation with IC_{50} values of 10 and 18 μmol/L in C666-1 and HK1 human nasopharyngeal carcinoma (NPC) cells, and slow tumor growth in the C666-1 xenograft model[95]. Moreover, ginsenoside Rh2 and Rg5 are all derived from *Panax ginseng* C. A. Mey. and have been shown to have anticancer effects in Jurkat L cells and MG-63 cells, respectively; both ginsenosides suppress the PI3K−Akt−mTOR pathway, which causes autophagy-dependent tumor cell death[96,97].

In addition, natural flavonoids have also been found to have antitumor activity in recent years. Morusin, an isopentenyl substituted flavonoid from *Morus alba*, has been reported to suppress PI3K−Akt and upregulate the phosphorylation of ERK, inhibiting A549 and NCI-H292 cell proliferation[98]. Similarly, 8-*C*-(*E*-phenylethenyl)quercetin has been reported to upregulate the phosphorylation of ERK in SW620 and HCT116 cells[99]. Eupalinolide A, a critical sesquiterpene of *Eupatorium lindleyanum*, has been reported to produce ROS and upregulate the phosphorylation of ERK, inhibiting the proliferation and migration in MHCC97-L and HCCLM3 cells[100]. Honokiol, a core component of TCM *Magnolia officinalis*, has been repeatedly reported to have antitumor activity. In neuroblastoma (NB), honokiol has been reported to inhibit PI3K−Akt−mTOR while activating ER stress, producing ROS, and upregulating the phosphorylation of ERK, inhibiting the proliferation and migration in neuro-2a cells[101]. In OS, honokiol can also produce ROS and upregulate the phosphorylation of ERK, inducing autophagy-dependent cell death and exerting promising antitumor efficacy *in vitro* and *in vivo*[102]. Moreover, alpha, 2′-dihydroxy-4,4′-dimethoxydihydrochalcone is identified from *Cedrela odorata*, which has been reported to upregulate the phosphorylation of MEK and ERK to activate autophagy, exerting profound antitumor efficacy *in vitro* and *in vivo*[103]. Natural medicine baicalein has been reported to upregulate the phosphorylation of ERK and Beclin-1, reducing the viability of OV cells[104]. Melatonin, a neurohormone that usually regulates circadian rhythms, has been reported to inhibit Akt and mTOR, upregulating Beclin-1 and LC3 while downregulating p62, reducing the viability of ELT3 human uterine leiomyoma cells[105]. In addition, CYT-Rx20 is a chemically synthesized *β*-nitrostyrene derivative that upregulates the phosphorylation of ERK, Beclin-1, and LC3 and exerts promising antiproliferative activity with IC_{50} values of 1.82 ± 0.05, 0.81 ± 0.04 and 1.12 ± 0.06 μmol/L in MDA-MB-231, MCF-7 and ZR75-1 cells[106]. Isoliquiritigenin is a chalcone isolated from TCM *Glycyrrhiza uralensis*, which has been reported to upregulate Beclin-1 and LC3 while downregulating p62, reducing the viability of OVCAR5 and ES-2 cells[107]. Similarly, oseltamivir, as a classic anti-hepatitis virus, was discovered to upregulate Beclin-1 and LC3 while downregulating p62 in Huh-7 and HepG2 cells, promising a new strategy for HCC

therapy[108]. Flubendazole, a classic repurposing FDA-approved anthelmintic drug available for cancer treatment, has been identified as an eva-1 homolog A (EVA1A) activator, which upregulated Beclin-1 and LC3-II while downregulated p62, inhibiting the proliferation and migration in MDA-MB-231 and MDA-MB-468 cells[109].

Importantly, several epigenetic regulators are implicated in the regulation of autophagy, which facilitates the discovery of more antitumor drugs. For instance, bromodomain-containing protein 4 (BRD4), a crucial molecule in cancer epigenetic regulation, has been reported to suppress the classical autophagy regulator AMPK[110,111]. Based on this discovery, a series of BRD4 inhibitors were designed and synthesized, among which compound **9f** has the best antiproliferative activity with IC_{50} values of 1.62 and 3.27 μmol/L in MCF-7 and MDA-MB-231 cells, triggering autophagy-dependent cell death by inhibiting BRD4 to activate AMPK[110]. Similarly, histone deacetylase (HDAC) is also a critical epigenetic regulator in cancer. A novel thieno[2,3-*d*]pyrimidine-based hydroxamic acid derivative **17c** has been reported to act as a BRD4−HDAC dual inhibitor, which triggered autophagy-dependent cell death by inhibiting BRD4 to activate AMPK, upregulating Beclin-1 and LC3-II while downregulating p62 in HCT116 cells, exerting promising antitumor efficacy *in vitro* and *in vivo*[112]. Moreover, F0911-7667 (Compd. **5**) has been reported to activate sirtuin-1 (SIRT1), an NAD^+-dependent deacetylase, activating AMPK to inhibit mTOR in U87MG and T98G cells. F0911-7667 activated PINK1 and Parkin to trigger mitophagy in GBM cells, exhibiting antiproliferative activity both *in vitro* and *in vivo*[113]. Similarly, sirtuin-3 (SIRT3) is also an NAD^+-dependent deacetylase, which plays an important role in autophagy[114]. For instance, 1-methylbenzylamino amiodarone was hit based on virtual screening as a novel SIRT3 activator, which upregulates Beclin-1, ATG4B, ATG5, and LC3-II while downregulates p62 to trigger autophagy-dependent cell death in MCF-7 cells[115]. Moreover, to develop novel SIRT3 activators, the lead compound ZINC03830212 was discovered through structure-based drug design and virtual screening. Subsequently, a series of ZINC03830212 derivatives were synthesized, among which compound **33c** (ADTL-SA1215) showed the optimal SIRT3-activating activity with E_{max} of 1.00 ± 0.07 μmol/L in MDA-MB-231 cells. Notably, compound **33c** not only upregulates Beclin-1 and LC3-II while downregulates p62 to trigger autophagy but also upregulates PINK1 and Parkin to trigger mitophagy in MDA-MB-231 cells, exhibiting antiproliferative activity both *in vitro* and *in vivo*[116].

δ-Valerobetaine, a metabolite that has been reported to upregulate PINK1 and LC3-II, triggering mitophagy and reducing proliferation in SW480 and SW620 cells[117]. Olanzapine, an antipsychotic drug available for cancer treatment, has been reported to inhibit NF-κB and upregulated LC3-II in T98G, LN229, and U87MG cells[118]. Solamargine, a natural product isolated from *Solanum nigrum* L., has been reported to inhibit LIF to upregulate miR-192-5p and downregulate its target protein CYR61, which decreases p-Akt to induce autophagy-dependent cell death in HepG2 and Huh-7 cells[119]. In addition, a variety of other small-molecule compounds have been developed to improve cancer treatment by targeting autophagy. For instance, a series of terpyridine derivatives have been synthesized and studied for antiproliferative activity; importantly, compound **6** showed remarkable antiproliferative activity in common solid tumors with an IC_{50} of 0.407 ± 0.028 μmol/L in MCF-7 cells and an IC_{50} of 0.243 ± 0.036 μmol/L in HCT116 cells; moreover, compound **6** also showed compelling antiproliferative activity in aggressive solid tumors with an IC_{50} of 0.114 ± 0.024 μmol/L in PANC-1 cells and an IC_{50} of 0.855 ± 0.248 μmol/L in U251 cells, and blood tumor with an IC_{50} of 0.916 ± 0.23 μmol/L in K562 human chronic myeloid leukemia (CML) cells. Then, further mechanism exploration found that compound **6** upregulated LC3 in PANC-1 cells[120]. Similarly, a series of spisulosine derivatives have been synthesized and evaluated for activity against BC, NSCLC, and CRC cells; the results showed that compound **26b** exerted reliable antiproliferative activity in all cells, especially in CRC such as Colo-205, LOVO, HT-29, DLD-1, SW-48 and SW-620 cells with IC_{50}s of 2.03, 3.33, 4.15, 4.46, 3.14, and 1.86 μmol/L. Then, further mechanism exploration found that compound **26b** upregulated LC3-II in DLD-1 cells[121]. In addition, liproxstatin-1 is a classical ferroptosis inhibitor that has been found to upregulate LC3 in K562 cells[122]. Nobiletin, a polymethoxy substituted flavonoid widely existing in citrus fruits, has been reported to increase LC3-II in A2780 and OVCAR3 cells[123]. Similarly, osthole, a natural coumarin from *Cnidium monnieri*, has been reported to increase LC3 and LC3-II, inhibiting proliferation in OVCAR3 and A2780 cells (Supporting Information Table S1)[124].

At present, many inducers of autophagy-dependent cell death with different scaffolds have been discovered. Among them, most of the inducers regulate upstream targets of autophagy, such as the ULK1 activator, AMPK activators, and mTOR inhibitors. Most of the autophagy inducers have satisfactory preclinical efficacy and are expected to provide new directions for cancer therapy.

2.2. *Targeting ferroptosis, cuproptosis, and disulfidptosis with small-molecule compounds in cancer*

2.2.1. *The key signaling pathways of ferroptosis, cuproptosis, and disulfidptosis*

Ferroptosis, a recently unveiled RCD subroutine, is initiated by iron overload and is propelled by the peroxidation process of highly unsaturated phospholipids (Fig. 3A)[125]. Currently, our understanding of ferroptosis suggests that depletion of glutathione suppresses GPX4, resulting in lipid peroxides accumulation that cannot be metabolized through GPX4-catalyzed glutathione reductase reactions[22,126]. This excess Fe^{2+} then causes the accumulation of ROS *via* the Fenton reaction, ultimately triggering ferroptosis[127]. There are two main pathways involved in inducing ferroptosis: one involves the system xc^- (cystine/glutamate antiporter)-glutathione-GPX4 signaling pathway. In this pathway, the system xc^- comprising solute carrier family 7 membrane 11 (SLC7A11) and solute carrier family 3 membrane 2 dimers embedded on the cell membrane surface with SLC7A11 as the main functional subunit, transports cysteine into cells for glutathione synthesis to assist GPX4 in degrading toxic lipid peroxides and inhibiting ferroptosis occurrence[126]. Therefore, inhibiting system xc^-, glutathione, or GPX4 expression can induce ferroptosis. The other way to trigger ferroptosis is through iron metabolism pathways where Fe^{3+} can be transported into cells *via* transferrin receptor 1[128]. Overexpression of transferrin receptor 1 leads to an increase in intracellular Fe^{3+} content causing iron overload and subsequently resulting in ferroptosis[128]. Additionally, pathways related to lipid peroxidation also contribute to ferroptosis as ROS accumulation within cells is a characteristic feature associated with it; ROS-induced lipid peroxide accumulation being the ultimate cause behind cellular ferroptosis[125,129]. Voltage-dependent anion channels play important regulatory roles during ROS metabolism processes with all three isoforms VDAC1−3 having been shown to play significant roles

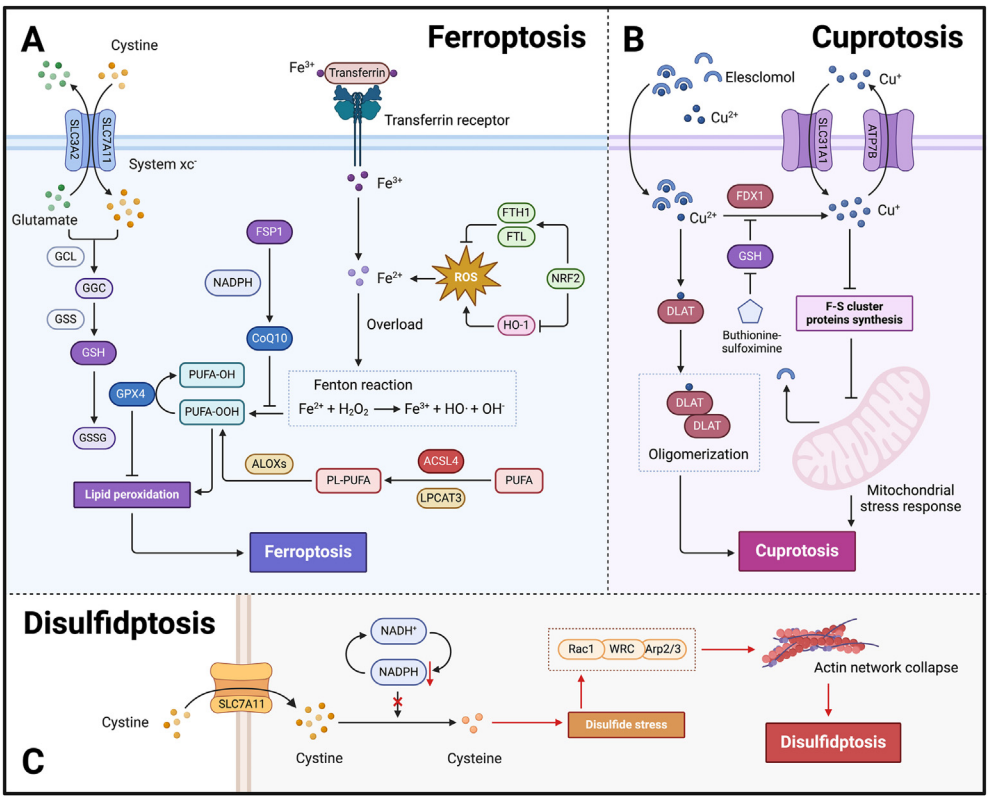

Figure 3 The key signaling pathways of ferroptosis, cuproptosis, and disulfidptosis. (A) Ferroptosis is primarily initiated by iron overload, excess Fe^{2+} causes ROS accumulation *via* the Fenton reaction, ultimately triggering ferroptosis. The system xc^- (cystine/glutamate antiporter) transports cysteine into cells for glutathione synthesis to assist GPX4 in degrading toxic lipid peroxides and inhibiting ferroptosis. Moreover, FSP1 is a kind of oxidoreductase of coenzyme Q10 (CoQ_{10}), which directly catalyzes CoQ_{10} regeneration in the presence of NAD(P)H and prevents the accumulation of lipid peroxidation to inhibit ferroptosis. (B) Cuproptosis is primarily triggered by copper overload, excess Cu^{2+} binds to acylated DLAT enzyme leading to abnormal oligomerization and increased insoluble DLAT ultimately inducing cell death. In addition, FDX1 facilitates the conversion of Cu^{2+} into the more pernicious Cu, resulting in instability and hindrance of Fe−S cluster protein synthesis, and ultimately mitochondrial stress response and cell death. (C) Disulfidptosis occurs mainly during glucose starvation when cysteine cannot convert to cystine due to insufficient NADPH, leading to disulfide stress, which activates Rac1−WRC−Arp2/3 to induce actin network collapse and cell death.

within the signal transduction pathway involved with cellular ferroptosis[130–132].

It is noteworthy that phase separation of ferroptosis suppressor protein 1 (FSP1), energy stress-mediated AMPK activation, plasticity of ether lipids, non-canonical glutamate−cysteine ligase activity, DHODH−GPX4 axis, lipid peroxidation−PKCβII−acyl-CoA synthetase long-chain family 4 positive-feedback axis, a novel monitoring mechanism for ferroptosis regulated by sex hormones but independent of GPX4, and pyrimidine bodies regulating pyrimidine metabolism flow and ferroptosis resistance are all essential for ferroptosis process[133–140].

Cuproptosis is a recently discovered type of RCD resulting from excessive copper accumulation. It was initially suggested in 2022[141]. The occurrence of cuproptosis, in contrast to other RCD forms (*e.g.*, apoptosis, ferroptosis, and pyroptosis), manifests through a uniquely intricate mechanism (Fig. 3B)[142]. Copper, as an essential trace element, plays critical roles in multiple physiological processes; however, its redox properties can have dual effects on cellular function. Therefore, maintaining intracellular copper levels within a reasonable range is critical for cellular homeostasis[143]. Both copper overload and deficiency can disrupt this balance and lead to cell death[141]. Cuproptosis occurs when there is an imbalance in copper homeostasis due to excessive accumulation of Cu^{2+} ions inside cells through extracellular carriers like Elesclomol that depend on mitochondrial respiration[144]. The molecular mechanism involves the binding of Cu^{2+} ions to acylated DLAT enzyme leading to abnormal oligomerization and increased insoluble DLAT causing cellular toxicity ultimately inducing cell death[145]. Additionally, FDX1 facilitates the conversion of Cu^{2+} into the more pernicious Cu, resulting in instability and hindrance of Fe-S cluster protein synthesis[143]. This results in mitochondrial stress response and cell death. In addition to copper ion carriers, other factors such as copper transporters (*e.g.*, SLC31A1) and copper efflux proteins (*e.g.*, ATP7B) can also influence the regulation of cuproptosis by altering the concentration of intracellular copper ions. Furthermore, glutathione, a copper chelator, inhibits cuproptosis while buthionine-sulfoximine promotes it by depleting glutathione[143]. With the rapid development of omics technologies, numerous research teams have utilized these techniques to identify several cuproptosis-related genes that regulate cuproptosis. Notably, *FDX1*, *PDHA1*, and other potential candidates have been identified. Moreover, these cuproptosis-related genes also serve as valuable biomarkers and prognostic indicators for tumors[146].

Disulfidptosis is a novel form of RCD resulting from abnormal accumulation of disulfide bonds between actin, a crucial cell structure for maintaining cell shape and survival (Fig. 3C)[147]. It

exhibits characteristics associated with sulfide stress. The element sulfur is an indispensable trace component within the human body, actively participating in a multitude of vital physiological processes, encompassing the crucial regulation of cellular redox homeostasis[148]. Sulfur primarily exists in cysteine and methionine residues, where cysteine residues exist as thiol or disulfides. Cytoplasmic thiols are predominantly present in glutathione, which degrades protein disulfide bonds[147]. Disulfide bonds are covalent bonds formed by oxidation of two cysteine residues and play a role in promoting protein folding and enhancing protein stability. However, abnormal accumulation of cytoplasmic disulfide bonds can disrupt cellular redox homeostasis, leading to sulfide stress-induced cytotoxicity[26]. The body primarily eliminates toxic disulfides through two different reduction pathways (the thioredoxin system and the glutathione system), both utilizing NADPH as a substrate whose reducing capacity is respectively regulated by GSR or TRXR1. The concept of disulfidptosis was first proposed in February this year[149]. Its molecular mechanism involves blocking cysteine reduction to cystine due to insufficient NADPH supply under glucose-starvation conditions, which results in the production of numerous disulfide bonds between actin molecules and induces disulfide stress[147]. This activation triggers the Rac/WRC-7 subunit's Arp2/3, causing disruption of the cellular skeleton and ultimately leading to the collapse of the actin network and cell death[149]. Importantly, genes associated with disulfidptosis have demonstrated usefulness in clinical diagnosis, prognosis prediction, and as treatment targets for liver cancer[150].

2.2.2. *Small-molecule compounds targeting ferroptosis, cuproptosis, and disulfidptosis*

Ferroptosis inducers (FINs) are currently categorized based on various mechanisms. One effective approach to initiate ferroptosis is by inhibiting system xc^-. This approach has garnered significant attention from researchers in recent years[4]. Thus, system xc^- inhibitor has been classified as class I FIN[151]. Erastin is closely linked to the discovery of ferroptosis and is currently utilized as a positive control in the study of ferroptosis[22]. Notably, erastin inhibits system xc^- to decrease glutathione and on the other hand directly binds to the voltage-dependent anion channels VDAC2 and VDCA3 to alter mitochondrial outer membrane permeability, leading to ROS production and lipid peroxidation accumulation, eventually inducing ferroptosis in multiple human cancer cells[22,152]. Subsequently, a series of erastin analogs were designed and synthesized to test the activities; among them, piperazine erastin and aldehyde erastin have been reported to show better activity in HT1080 cells with IC_{50}s of 0.9 μmol/L and 8 nmol/L, respectively; and exert the better antiproliferative activity and higher stability *in vivo*[153]. Similarly, compound **8** is a potent PKM2 inhibitor modified based on the lead compound NP-1, which was found to disrupt the interaction of PKM2 and VDAC3 and inhibit multiple cancer cell proliferation with IC_{50} values of 5.19 ± 1.74, 5.40 ± 1.14 and 4.75 ± 1.15 μmol/L in HCT116, MCF-7 and H1299 cells, respectively[154]. And, six C-3′—C-6″ biflavonoids, a series of natural compounds extracted from *Selaginella trichoclada*, have been reported to inhibit MCF-7 cells, among which compound RF-A exhibited the best activity with an IC_{50} of 11.89 μmol/L; in addition, RF-A activated VDAC2 to downregulate NEDD4 and produced ROS with lipid peroxidation accumulation, resulting in ferroptosis in MCF-7 cells[155]. Inspired by erastin, compound **8** has also been found to inhibit system xc^- and decrease glutathione to induce ferroptosis, obtaining greater efficacy[156]. Moreover, in diffuse large B cell lymphoma (DLBCL), imidazole ketone erastin, an analog of erastin with better activity and stability, has been reported to be a novel system xc^- inhibitor, which depleted glutathione to induce ferroptosis, exhibiting antiproliferative activity both *in vitro* and *in vivo*[157]. A novel class of FINs has been discovered to successfully block cancer stem cell function, hence slowing tumor progression; among them, compound **4** has been found to inhibit system xc^- to induce ferroptosis in MDA-MB-468 cells[158]. To develop FIN with new scaffolds, the lead compound FA-S was hit based on phenotypic screenings. Thus, a series of 2-(trifluoromethyl)benzimidazole derivatives were synthesized, among which FA16 showed the optimal antiproliferative activity with an IC_{50} of 1.33 ± 0.04 μmol/L in HepG2 cells, and slowed tumor progression under low toxicity *in vivo*. FA16 has been reported to induce ferroptosis by inhibiting system xc^- and may also be suitable for ferroptosis-related studies *in vivo*[159]. Of note, SLC7A11 and solute carrier family 3 membrane 2 are important components of system xc^-. In CRC, 2-imino-6-methoxy-2*H*-chromene-3-carbothioamide has been reported to upregulate the phosphorylation of AMPK to suppress the SLC7A11 and deplete glutathione, triggering ferroptosis and exerting promising antiproliferative activity with IC_{50} values of 50.2 and 44.5 μmol/L in DLD-1 and HCT116 cells[160]. Talaroconvolutin A (TalaA), a metabolite produced by *Talaromyces purpureogenus*, has been reported to produce ROS, leading to lipid peroxidation, downregulating SLC7A11 while upregulating arachidonate lipoxygenase 3, inducing ferroptosis to inhibit proliferation with IC_{50} values of 9.23, 8.15 and 5.82 μmol/L in HCT116, SW480 and SW620 cells and slow tumor growth in the HCT116 xenograft model[161]. 18β-Glycyrrhetinic acid, a natural triterpenoid extracted from Licorice, has been reported to downregulate SLC7A11 to deplete glutathione and produce ROS with the accumulation of Fe^{2+} and lipid peroxidation, triggering ferroptosis in human MDA-MB-231 cells[162]. Importantly, sorafenib, the first FDA-approved multi-target anticancer drug, is still used in the clinical treatment of HCC and advanced renal cell carcinoma (RCC)[163]. In conjunction with a variety of modulators associated with cell death, sorafenib was found to induce ferroptosis, primarily by inhibiting system xc^- in HCC[164,165]. Ursolic acid, a natural pentacyclic triterpene existing in various herbals, has been reported to inhibit SLC7A11 to trigger ferroptosis when combined with sorafenib, mitigating the resistance of sorafenib alone[166]. In addition, artesunate, a derivative of artemisinin, can also effectively overcome chemoresistance caused by sorafenib and restore drug sensitivity in HCC treatment[167].

GPX4 is a critical regulatory enzyme in ferroptosis that converts glutathione to oxidized glutathione and reduces lipid peroxides; therefore, inhibiting GPX4 results in lipid peroxides accumulation to trigger ferroptosis, which could be more effective than inhibition of system xc^- in cancer therapy[168,169]. Notably, the GPX4 inhibitor or degrader has been classified as Class II FIN[151]. RSL3, a synthetic lethal screening-based inhibitor of tumors with *RAS*, was subsequently identified as a typical Class II FIN[170]. RSL3 has been reported to produce ROS and inhibit GPX4, inducing ferroptosis and exerting compelling antiproliferative activity with IC_{50} values of 4.084, 2.75 and 12.38 μmol/L in human CRC cells, respectively[171]. Moreover, a series of RSL3 analogs were designed and synthesized, among which compound **24** has been identified as a novel GPX4 inhibitor, showing antiproliferative activity with an IC_{50} of 0.0026 μmol/L in WSU-DLCL2 cells; compound **24** greatly improves the metabolic stability of RSL3 *in vivo* and may be more suitable for ferroptosis-related study *in vivo*[172]. Similarly, based on the scaffold hopping method, a series of novel GPX4 inhibitors from the lead compound RSL3 have been explored, and discovered the optimal scaffolds—benzo[*b*]thiophene-3-yl and indole-3-yl—for ferroptosis selectivity. Then, based on this direction for further

modification, obtained compound **26a**, which has shown the promising inhibitory effect of GPX4 and lipid peroxides accumulation. Compound **26a** effectively induced ferroptosis and exerted compelling antiproliferative activity with IC_{50} values of 0.78 ± 0.01 and 6.90 ± 0.21 μmol/L in 4T1 and MCF-7 cells, respectively; and, compound **26a** also slowed tumor progression in the 4T1 syngeneic model[173]. In addition, ML162 and ML210, the synthetic lethal screening-based inhibitors of tumors with IC_{50} values of 0.025 and 0.071 μmol/L in BJeLR cells with $HRAS^{G12V}$ mutant, were identified as common Class II FIN due to the inhibition of GPX4[174]. Inspired by ML210, masked nitrile oxides have been discovered to exert high selectivity for GPX4, providing a new clue for the development of GPX4 inhibitors[175]. Based on promising masked nitrile oxides, a series of nitroisoxazole-containing spiro[pyrrolidin-oxindole] derivatives were designed and synthesized, among which compound **3d** exerting promising antiproliferative activity with an IC_{50} of 0.12 μmol/L in MCF-7 cells and slowing tumor progression in the MCF-7 xenograft model; and, compound **3d** has been identified as MDM2-GPX4 specific dual inhibitor, inducing apoptosis and ferroptosis *in vitro* and *in vivo*[176]. Furthermore, based on ML210, a series of GPX4 degraders were designed and synthesized, among which DC-2 exerted the optimal degradation activity with a DC_{50} of 0.03 μmol/L in HT1080 cells; and, DC-2 exerted compelling antiproliferative activity with IC_{50} values of 0.1, 0.3 and 0.2 μmol/L in HT1080, Calu-1 and A375 cells, and slowed tumor growth in the HT1080 xenograft model, while effectively improving safety *in vitro* and *in vivo*[177]. Similarly, based on RSL3, a series of GPX4 degraders were designed and synthesized, among which compound **8e** exerted the optimal degradation activity with DC_{50}s of 23.26 nmol/L in HT1080 cells and 136 nmol/L in Calu-1 cells; and, compound **8e** exerted compelling antiproliferative activity with IC_{50} values of 58 and 25 nmol/L in HT1080 and Calu-1 cells, and even showed high efficacy with an IC_{50} of 1.56 μmol/L in gefitinib-resistant H1650 cells[178]. Both DC-2 and compound **8e** have been reported to degrade GPX4, resulting in lipid peroxides accumulation to trigger ferroptosis, slowing tumor progression under low toxicity[177,178]. Altretamine, a classical FDA-approved antineoplastic agent, has been identified as a novel GPX4 inhibitor, accumulating ROS to induce ferroptosis in U-2932 cells[179]. Additionally, certain natural compounds induce ferroptosis and inhibit GPX4, thereby functioning as anticancer agents. For instance, Jiyuan oridonin A is a natural product with the chemical skeleton of *ent*-kaurane diterpenoids from Jiyuan *Rabdosia rubescens*; its derivative compound **a2** has been reported to downregulate GPX4 to induce ferroptosis in multiple GC cells, exerting promising antiproliferative activity *in vitro* and *in vivo*[180]. Ponicidin, a natural product extracted from *R. rubescens*, has been reported to directly bind to glutathione and downregulate GPX4 to induce ferroptosis, exerting compelling antiproliferative activity with an IC_{50} of 20.84 μmol/L in SW1990 cells[181]. Dihydroisotanshinone I, a natural product identified from *S. miltiorrhiza* Bunge, has been reported to downregulate GPX4 to trigger ferroptosis in MCF-7 and MDA-MB-231 cells, exerting compelling antiproliferative activity *in vitro* and *in vivo*[182]. Importantly, DMOCPTL, a derivative of the natural product parthenolide, has been reported to be the first compound to directly bind and ubiquitinate GPX4, downregulating GPX4 to induce ferroptosis and inhibit the proliferation in MDA-MB-231 and SUM159 cells. Moreover, compound **13** was modified from DMOCPTL, which greatly improved water solubility and slowed tumor progression under low toxicity in the orthotopic 4T1 mouse model[183]. Similarly, bufotalin, a natural product extracted from toad venom, has been reported to ubiquitinate and downregulate GPX4 to induce ferroptosis, exerting compelling antiproliferative activity with an IC_{50} of 4.21 ± 0.90 μmol/L in A549 cells, and slowed tumor growth in the A549 xenograft model[184]. Cisplatin, a classical chemotherapeutic drug, has been reported to suppress GPX4, leading to glutathione depletion, which induced ferroptosis in A549 and HCT116 cells to suppress proliferation[185]. Sulfasalazine has been found to effectively restore drug sensitivity in head and neck cancer (HNC) cells when cisplatin resistance develops after prolonged treatment[186]. Apatinib, a classic repurposing anti-angiogenic agent drug available for GC treatment, has been reported to downregulate GPX4 and decrease glutathione, leading to lipid peroxidation to induce ferroptosis and exert antitumor efficacy *in vitro* and *in vivo*, and overcome chemoresistance that caused by cisplatin and 5-fluorouracil (5-FU)[187]. Furthermore, several compounds trigger ferroptosis by downregulating both system xc^- and GPX4. For instance, WJ460 has been reported to downregulate both system xc^- and GPX4, resulting in lipid peroxidation, inducing ferroptosis, and suppressing MIA PaCa-2 cell proliferation with an IC_{50} of 20.92 ± 1.02 nmol/L[188]. Similarly, lenvatinib, a classical multi-kinase anticancer drug, has been reported to downregulate both system xc^- and GPX4, inducing ferroptosis and suppressing proliferation in human HCC cells[189].

Of note, the compound that consumes CoQ_{10} has been classified as Class III FIN[190]. CoQ_{10} is a typical antioxidant that prevents the accumulation of lipid peroxidation and has been known as a critical negative regulator in ferroptosis[190,191]. FIN56 is a typical Class III FIN that degrades GPX4 through the mevalonate pathway and binds to squalene synthase to deplete CoQ_{10}, increasing the level of ferroptosis[192]. FSP1 has been found as a kind of oxidoreductase of CoQ_{10}, which directly catalyzes CoQ_{10} regeneration in the presence of NAD(P)H and prevents the accumulation of lipid peroxidation to suppress ferroptosis[193,194]. Therefore, iFSP1, an inhibitor of FSP1 that directly binds at Phe360 of FSP1, has been identified as a Class III FIN, triggering ferroptosis in HT1080 cells[194]. Notably, icFSP1 is the first targeted inhibitor of FSP1, which induces phase separation of FSP1, inducing ferroptosis to exert antitumor efficacy *in vitro* and *in vivo*; due to mechanism specificity, it can also be combined with GPX4 inhibitors or other types of FINs to play a synergistic role in enhancing ferroptosis[133]. Moreover, curcumin is a natural product extracted from *Curcuma longa*, andrographis is a Chinese herbal medicine, both of which have been reported previously to exhibit antitumor activity. Recently, curcumin and andrographis have been reported to synergistically inhibit GPX4 and FSP1, inducing ferroptosis and suppressing proliferation and migration in SW480 and HCT116 cells[195]. In addition, statins are also typical Class III FINs that suppress the mevalonate pathway to downregulate GPX4, leading to lipid peroxidation and ROS accumulation, triggering ferroptosis in multiple cancers[196]. For instance, simvastatin exerted promising anti-TNBC efficacy *in vitro* and *in vivo via* inducing ferroptosis[197]. And, lovastatin inhibits the proliferation and migration of NSCLC *in vitro* and *in vivo*, slowing the progression of NSCLC[198].

Importantly, the compound that induces lipid peroxidation from overloading iron or polyunsaturated fatty acid has been classified as Class IV FIN[190]. $FINO_2$ is a typical Class IV FIN that indirectly suppresses GPX4 and oxidizes ferrous iron and lipidome, leading to lipid peroxidation to induce ferroptosis[199]. The efficacy of $FINO_2$ is similar to several classic FDA-approved anticancer agents, implying the clinical potential for future cancer therapy[200]. Moreover, artemisinin, a natural product famous for antimalarial activity, has been also identified as a Class IV FIN; artemisinin derivative

dihydroartemisinin has been reported to induce ferritin autophagy to unstable iron, inhibiting GPX4 to induce ferroptosis, showing promising cancer therapeutic potential *in vitro* and *in vivo*[201]. DAT-coumarin hybrids have been explored for antitumor activities; among them, compound **A**-induced ferroptosis and exerted promising antiproliferative activity with IC_{50}s of 0.17 and 7.51 μmol/L in HT-29 and MDA-MB-231 cells under hypoxia condition, respectively[202]. Similarly, artemisinin derivative artesunate has been reported to increase ROS and decrease glutathione, triggering ferroptosis and inhibiting the proliferation of HNC cells[203]. And, artemisinin derivative artesunate has also been reported to exert antitumor efficacy in OV and DLBCL *via* inducing ferroptosis[204]. Palmitic acid is a saturated fatty acid that overloads iron with ROS and lipid peroxidation accumulation, triggering ferroptosis and inhibiting the proliferation of CRC cells *in vitro* and *in vivo*[205]. Nuclear factor erythroid 2-related factor 2 (NRF2), a negative regulator of ferroptosis, acts as a transcription factor that directly regulates ROS metabolism-related proteins such as heme oxygenase-1 (HO-1) to decrease lipid peroxidation and the level of ferroptosis[206]. Erianin is a bioactive ingredient extracted from *Dendrobium chrysotoxum* Lindl, has been reported to inhibit NRF2 to increase ROS and decrease glutathione with the accumulation of ferrous iron, triggering ferroptosis in KU-19-19 and RT4 bladder cancer (BLCA) cells and exerting promising antitumor efficacy *in vitro* and *in vivo*[207]. Similarly, erianin triggered ferroptosis to reduce the viability of NCI-H460 and H1299 cells, and slow tumor growth in the NCI-H460 xenograft model[208]. *S*-3′-Hydroxy-7′,2′,4′-trimethoxyisoxane, a natural product identified from *Dalbergia odorifera* T. Chen, has been reported to suppress the NRF2/HO-1 axis to increase ROS and decrease glutathione with the accumulation of Fe^{2+} and lipid peroxidation, downregulating GPX4 to induce ferroptosis and exert compelling antiproliferative activity with an IC_{50} of 7.5 ± 0.52 μmol/L in A549 cells[209]. Moreover, cetuximab, a classic FDA-approved anticancer agent for metastatic CRC, has been reported to suppress the NRF2/HO-1 axis to increase RSL3-induced ROS production and ferroptosis in KRAS mutant CRC cells[210]. In addition, siramesine and lapatinib also classic agents, have been reported to synergistically downregulate HO-1 to increase iron and produce ROS, leading to lipid peroxidation to induce ferroptosis in A549 and U87MG cells[210]. Of note, the level of iron and ROS affect how HO-1 behaves in ferroptosis; when the level is too high, HO-1 switches from acting as a negative regulator to a positive regulator[211]. Shuganning injection, a Chinese patent medicine that has been reported to promote HO-1-dependent Fe^{2+} accumulation, increase ROS and lipid peroxidation, induce ferroptosis in MDA-MB-231 and MDA-MB-468 cells, and exert profound antitumor efficacy *in vitro* and *in vivo*[212]. Honokiol upregulates HMOX1 (HO-1), leading to lipid peroxidation to induce ferroptosis in THP-1, U-937, and SKM-1 AML cells[213]. Moreover, shikonin has been reported to overcome chemoresistance caused by cisplatin prolonged treatment in OV, restoring drug sensitivity and upregulating HMOX1 (HO-1) with the accumulation of Fe^{2+} to induce ferroptosis *in vitro* and *in vivo*[214]. Juglone, a natural naphthoquinone existing in *Carya cathayensis*, has been reported to upregulate HMOX1 and deplete glutathione with Fe^{2+} and lipid peroxidation accumulation, inducing ferroptosis to reduce the viability and inhibit invasion in Ishikawa endometrial cancer cells[215]. The signal transducer and activator of transcription 3 (STAT3) is a transcription factor that is closely associated with multiple cancer-related pathways, especially oxidative metabolism, which may participate in the regulation of ferroptosis[216]. For instance, PPVI has been reported to suppress STAT3 to inhibit *GPX4* transcription, inducing ferroptosis to inhibit the proliferation and invasion in HCCLM3 and Huh-7 cells[217]. Moreover, W1131 is a novel STAT3 inhibitor, which directly suppresses STAT3 to inhibit *GPX4*, *SLC7A11*, and ferritin heavy chain 1 (*FTH1*) transcription, producing ROS and depleting glutathione with Fe^{2+} and lipid peroxidation accumulation, inducing ferroptosis to reduce the viability of AGS and MGC-803 cells and slow tumor progression in the MGC-803 xenograft model[218]. A novel aroyl diheterocyclic pyrrole derivative compound **15** has been found to downregulate GPX4 and FTH1 with the accumulation of Fe^{2+}, inducing ferroptosis and exhibiting antiproliferative activity with IC_{50} values of 10.06 and 2.852 nmol/L in U-87MG and OVCAR-3 cells[218]. Baicalin, a natural product extracted from *Scutellaria baicalensis*, has been reported to suppress FTH1 with ROS accumulation, inducing ferroptosis in 5637 and KU-19-19 cells and exerting promising antitumor efficacy *in vitro* and *in vivo*[219]. 6-Gingerol, a major constituent of *Zingiber officinale* Roscoe, has been reported to produce ROS and accumulate Fe^{2+}, reducing tumor viability and progression *in vitro* and *in vivo*[220]. Alterperylenol, a natural product extracted from *Vitis quinquangularis*, has been reported to produce ROS and induce lipid peroxidation from overloading iron, triggering ferroptosis in HepG2 cells and exerting profound antitumor efficacy *in vitro* and *in vivo*[221]. 6-Shogaol, a natural product extracted from ginger, has been reported to deplete glutathione with the accumulation of Fe^{2+} and lipid peroxidation, upregulating HMOX1 and downregulating SLC7A11, GPX4, and ferritin light chain (FTL) to induce ferroptosis and reduce the viability of Ishikawa endometrial cancer cells with an IC_{50} of 24.91 μmol/L[222]. In addition, auriculasin is extracted from *Flemingia philippinensis*, which has been reported to produce ROS with the accumulation of Fe^{2+}, inducing ferroptosis and inhibiting proliferation and migration in HCT116 and SW480 cells[223]. Chidamide is a histone deacetylase inhibitor that has been found to produce ROS with the accumulation of Fe^{2+}, downregulating GPX4 to induce ferroptosis and inhibit the proliferation of TU212 and AMC-HN-8 human laryngeal cancer (LSCC) cells, and slowing tumor growth *in vivo*[224].

Additionally, several other compounds are implicated in the regulation of ferroptosis, which facilitates the discovery of more antitumor drugs. Terpenoids are a class of compounds that have good anticancer activity in natural products[225]. Albiziabioside A is a triterpenoid saponin with antitumor activity, whose derivatives are being explored continuously; among them, compound **D13** has been reported to exert the highest antiproliferative activity with an IC_{50} of 5.19 ± 0.08 μmol/L in HCT116 cells and the lowest toxicity with IC_{50} values of greater than 20 μmol/L in multiple human normal cells. And, compound **D13** produced ROS and activated p53, inhibiting GPX4 and leading to lipid peroxidation to induce ferroptosis[226]. Surprisingly, p53 directly suppresses *SLC7A11* gene transcription, a crucial component of system xc^-[227]. Moreover, kayadiol, a diterpenoid extracted from *Torreya nucifera*, has been identified as a p53 activator to suppress SLC7A11, which produced ROS and depleted glutathione, downregulating GPX4 to induce ferroptosis in Extranodal natural killer/T cell lymphoma cells[228]. Flubendazole, a classic repurposing non-oncology drug available for multiple cancer treatment, has been reported to activate p53 to suppress *SLC7A11* gene transcription, downregulating GPX4, inducing ferroptosis to inhibit the proliferation of castration-resistant PC-3 and DU145 cells and slow tumor growth in the PC-3 xenograft model[229]. MMRi62 is a chemically synthesized MDM2−MDM4-targeting small molecule, has been found to degrade mutant p53 and FTH1, inducing ferroptosis to inhibit PNAC-1 and BxPC-3 cell proliferation and migration and slow tumor progression and metastasis in the orthotopic PNAC-1 and

BxPC-3 xenograft models[230]. Eupaformosanin is a natural product extracted from *Eupatorium cannabinum* Linn., which has been reported to suppress mutant p53 and SLC7A11, produce ROS, and deplete glutathione, increasing iron and downregulating GPX4 to induce ferroptosis in MDA-MB-231 cells[231]. Isothiocyanate sulforaphane, a natural product extracted from multiple cruciferous vegetables, has been reported to deplete glutathione and downregulate GPX4, leading to lipid peroxidation to induce ferroptosis in U-937 cells[232]. Gallic acid, a natural product extracted from some edible mushrooms and herbal medicines, has been reported to induce lipid peroxidation and ferroptosis in HeLa, H446, and SH-SY5Y cells[233]. Diplacone is a natural product extracted from *Paulownia tomentosa*, which has been reported to produce ROS, leading to lipid peroxidation and upregulating ATF3—a critical regulator in iron metabolism—to induce ferroptosis in A549 cells[234]. QD394 is a quinazolinedione that induces ROS production and has been reported to suppress STAT3 and decrease GPX4, showed reliable antiproliferative activity with IC_{50} values of 0.64, 0.34 and 0.9 μmol/L in MIA PaCa-2, PANC-1, and BxPC-3 cells, respectively. In addition, QD394-ME was obtained by methyl modification from QD394, which greatly improved metabolic stability and reduced toxicity with similar functions and activities in PANC-1 and BxPC-3 cells[235]. Notably, eprenetapopt (APR-246) is a classical FIN that is under clinical trial, which depletes glutathione with ROS and lipid peroxidation accumulation to trigger ferroptosis in multiple cancer cells[236,237]. Furthermore, APR-246 also has been found the potential for esophageal cancer, AML, and DLBCL therapy[236−239]. Siramesine and lapatinib are classical chemotherapeutic drugs that have been reported to be synergistically causing lipid peroxidation to induce ferroptosis and reduce the viability of MDA-MB-231 and SKBr3 cells[240]. Moreover, doranidazole and misonidazole are 2-nitroimidazoles, have been found to produce ROS to induce ferroptosis in hypoxic glioma stem cells[241]. In addition, chlorido [*N*,*N*′-disalicylidene-1,2-phenylenediamine]iron(III) complexes, have been found to produce ROS to induce ferroptosis in HL-60 and NB1 cells[242]. Similarly, chlorido[4-carboxy-1,2-disalicylideneam inobenzene]iron(III) has been identified as an excellent lead structure, whose derivatives also induce ferroptosis and reduce the viability of HL-60 cells (Supporting Information Table S2)[243].

Currently, common drug targets for ferroptosis include system xc^- (including SLC7A11), GPX4, FSP1, HMOX1, FTH1, and FTL, with strategies for regulating GPX4 appearing to be more popular. Targeting ferroptosis has gradually become one of the potential apoptosis alternative therapies for cancer. Further, despite the paucity of studies on the discovery of drugs that induce cuproptosis and disulfidptosis to treat cancer, it is anticipated that as the underlying mechanisms of the two processes are gradually clarified, compounds that target the critical cuproptosis and disulfidptosis proteins will be developed, with the potential to advance cancer therapy in the future.

2.3. *Targeting necroptosis with small-molecule compounds in cancer*

2.3.1. *The key signaling pathways of necroptosis*

Necroptosis is characterized by morphological features of cellular necrosis and molecular characteristics that are independent of caspase activity (Fig. 4)[5,244,245]. The pathogenesis of various human diseases, including cancer, is significantly influenced by it. RIPK1, RIPK3, and the executioner protein MLKL are core components tightly regulated within the necroptosis signaling pathway[4,246]. Multiple pathways can trigger necroptosis, with the most well-known being activation mediated by TNF and its receptor (TNFR1)[247,248]. Upon TNFR1-TNF binding, complex I is formed consisting of RIPK1, TNFR1-associated death domain protein (TRADD), TNF-receptor-associated factor (TRAF2/5), and cIAP1/2[5]. RIPK1 can be ubiquitinated by cIAP1/2 and LUBAC or deubiquitinated by CYLD[249]. Deubiquitinated RIPK1 forms complex II with caspase-8, TRADD, and Fas-associated protein with death domain[4,244]. Apoptosis activation takes place upon the activation of caspase-8 within complex II. Activation of downstream apoptotic signaling pathways occurs when caspase-8 is activated within complex II. In contrast, when caspase-8 activity is inhibited, there is an association between RIPK1 and RIPK3 through their homotypic interaction motifs (RHIM)[248]. Subsequently, phosphorylation and trans-phosphorylation occur on both RIPK1 and RIPK3. Phosphorylated RIPK3 recruits MLKL which then undergoes phosphorylation to form a necrosome structure[245,250]. Ultimately, phosphorylated MLKL undergoes oligomerization and translocation to the plasma membrane where it forms pore complexes leading to damage-associated molecular pattern (DAMP) secretion as well as cellular swelling and membrane rupture triggering necroptosis[4,244].

In HCC specifically, activation of the necrosome can result in two distinct cellular outcomes: lethal or sublethal necroptosis[251]. As a molecular switch governing these alternative modes in liver cells, NF-κB mediates this reprogramming process. Activation of the necrosome accompanied by low expression levels of RIPK3 contributes to HCC development while inactive NF-κB signals prevent it[251]. Moreover, introducing excess sorbitol dehydrogenase into HCC cells enhances necroptotic signals through regulation of lactate dehydrogenase A expression and mitochondrial dynamics, and bypasses energy production pathways, resulting in growth inhibition and suppression of stemness in liver cancer cells[252]. Furthermore, the occurrence of HCC has been found to be correlated with increased levels of both necroptosis and cellular senescence within liver cells[253,254].

2.3.2. *Small-molecule compounds targeting necroptosis*

TNF-α is an upstream critical protein in necroptosis, thus, there are several compounds that induce necroptosis *via* activating TNF-α. For instance, cisplatin is a classical chemotherapeutic drug, which has been found to induce necroptosis in L929 cells. On one hand, cisplatin increased TNF-α autocrine to activate downstream regulators RIPK1, RIPK3, and MLKL; on the other hand, cisplatin activated RIPK1 and CypD, a critical regulator to open MPTP, leading to mitochondrial membrane depolarization and the increase of ROS to trigger necroptosis[255]. Berberine, has been reported to increase cisplatin-induced necroptosis; cisplatin combined with berberine greatly increased the phosphorylation of RIPK3 and MLKL, inducing necroptosis and inhibiting antiproliferation of OVCAR3 cells[256]. Moreover, 5-FU is also a classical chemotherapeutic drug in CRC therapy, which increased TNF-α autocrine and activated RIPK1 when combined with caspase inhibitor IDN-7314, showing CRC therapeutic potential *in vitro* and *in vivo*[257]. Emodin, an anthraquinone extracted from Radix et Rhizoma Rhei, has been reported to upregulate the TNF-α, RIPK1, RIPK3, and MLKL to induce necroptosis, exerting antiproliferative activity with an IC_{50} of 22.44 μmol/L in U251 cells and slowing tumor growth in the U251 xenograft model[258].

Numerous compounds have been discovered to regulate the primary necroptosis regulators, RIPK1, RIPK3, and MLKL, which cause necroptosis as a result. For instance, Ophiopogonin D′, a natural steroidal saponin extracted from *Ophiopogon japonicus*, has been reported to significantly induce necroptosis *via* two parallel

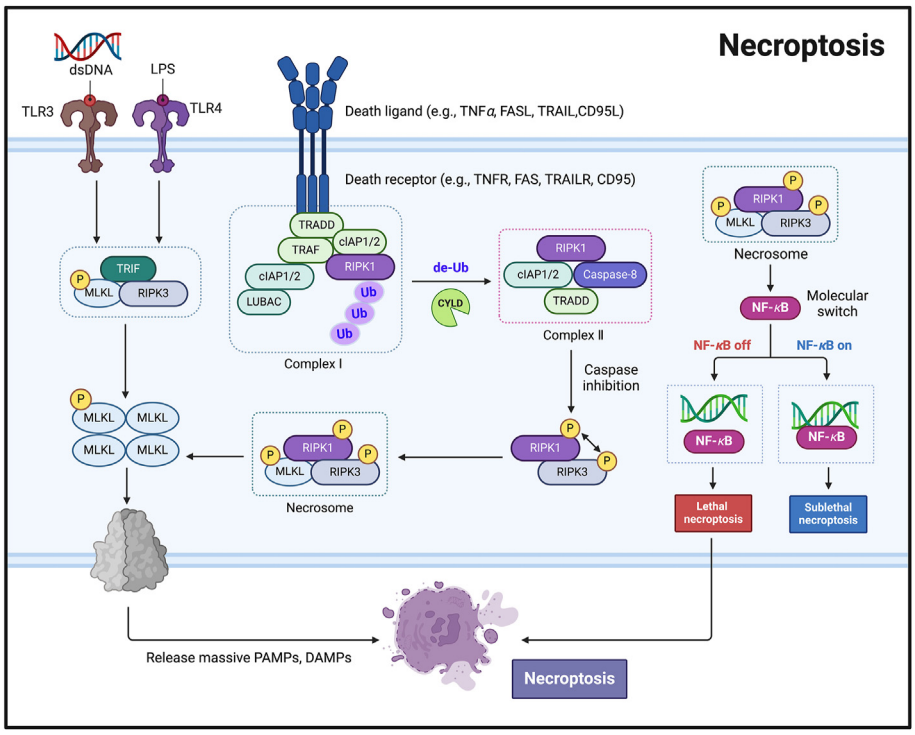

Figure 4 The key signaling pathways of necroptosis. Necroptosis is initiated by the binding of death ligand and death receptor, which activates RIPK1, TRADD, TRAF, and cIAP1/2. RIPK1 can be ubiquitinated by cIAP1/2 and LUBAC or CYLD. Deubiquitinated RIPK1 forms complex II with caspase-8, TRADD, and Fas-associated protein with death domain. When caspase-8 activity is inhibited, phosphorylation and trans-phosphorylation occur on both RIPK1 and RIPK3. Phosphorylated RIPK3 recruits MLKL which then undergoes phosphorylation to form a necrosome. Ultimately, phosphorylated MLKL undergoes oligomerization and translocation to the plasma membrane where it forms pore complexes leading to DAMP secretion, triggering necroptosis.

pathways, namely activating RIPK1 and upregulating RIPK3 to enhance the interaction with MLKL, respectively; and, Ophiopogonin D′ also exerted reliable antiproliferative activity with an IC_{50} of 5.34 μmol/L in LNCaP cells[259]. Rubiarbonol B, a triterpenoid isolated from *Rubia philippinesis*, has been reported to produce ROS and upregulate the phosphorylation of RIPK1, which further increases the phosphorylation of RIPK3 and MLKL to trigger necroptosis in HT-29 cells[260]. Shikonin has been reported to produce ROS to activate RIPK1 and RIPK3, inducing necroptosis and inhibiting the proliferation of EJ, J82, T24 and BIU87 cells[261]. Bufalin has been reported to upregulate the RIPK1 and RIPK3, producing ROS and activating PARP-1, which induced necroptosis and inhibited the proliferation of MCF-7 and MDA-MB-231 cells and the MDA-MB-231 xenograft model[262]. Moreover, neoalbaconol is a sesquiterpenoid extracted from *A. confluens*, which has been reported to enhance the interaction of RIPK1 with RIPK3 in C666-1 and HK1 cells, triggering necroptosis and reducing tumor progression and viability *in vitro* and *in vivo*[95]. Triptolide, a diterpenoid extracted from *Tripterygium wilfordii* Hook F, has been reported to upregulate RIPK1, RIPK3, and MLKL phosphorylation to induce necroptosis, reducing the viability of Huh-7 and Hep3B cells with IC_{50} values of 17.25 and 33.97 ng/mL, respectively[263]. Fruticuline A is a natural diterpene from *Salvia lachnostachys*, which has been reported to activate RIPK1 to induce necroptosis, exerting antiproliferative activity in HepG2 and MCF-7 cells[264]. Similarly, polymatin B, a natural sesquiterpene lactone extracted from *Smallanthus sonchifolius*, has been reported to produce ROS and activate RIPK1 to induce necroptosis and inhibit proliferation in ADR/CEM5000 cells with an IC_{50} of 1.3 ± 0.2 μmol/L[265]. Delta-tocotrienol, a member of vitamin E, has been reported to upregulate the phosphorylation of RIPK1 and MLKL to induce necroptosis, reducing the viability of DU145 and PC-3 cells. Delta-tocotrienol can also overcome chemoresistance caused by docetaxel and restore drug sensitivity in PRAD treatment[266]. Celastrol is methide triterpenoid with antitumor activity in glioma, whose derivatives are being explored continuously; among them, compound **6i** has been reported to exert the highest antiproliferative activity with an IC_{50} of 0.94 ± 0.45 μmol/L in U251 cells and upregulate RIPK1, RIPK3 and MLKL phosphorylation to induce necroptosis. And, compound **6i** has been also reported to cross the blood−brain barrier and inhibit tumor proliferation in the U251 zebrafish xenograft model[267]. Obatoclax is a BCL-2 inhibitor, which has been found to activate RIPK1 and RIPK3, inducing necroptosis and slowing tumor growth in the rhabdomyosarcoma chicken chorioallantoic membrane xenograft model[268]. RETRA is a known compound with anticancer potential, which has been found to produce ROS and upregulate the phosphorylation of RIPK1, RIPK3, and MLKL to induce necroptosis and inhibit proliferation in SiHa and C33A cervical cancer (CC) cells[269,270]. Geldanamycin is the first natural HSP90 inhibitor, whose derivative DHQ3 also inhibits Hsp90; subsequently, DHQ3 has been found to upregulate the RIPK1, RIPK3, and MLKL to induce necroptosis, reducing the viability of MDA-MB-231 cells and the xenograft model[271]. TMQ0153 is a tetrahydrobenzimidazole derivative that has been reported to produce ROS and activate RIPK1 to induce necroptosis, and exert antiproliferative activity in K562 human CML cells and zebrafish xenograft model[272]. Moreover, compound **3u** is a naphthyridine derivative that has been reported to upregulate the

phosphorylation of RIPK1 and MLKL to induce necroptosis, exert excellent antiproliferative activity with an IC_{50} of 1.52 ± 0.10 μmol/L in A375 cells[273]. In addition, IMB5036 is a chemically synthesized pyridazinone compound that has been reported to upregulate RIPK1, RIPK3, and MLKL phosphorylation to induce necroptosis, reducing the viability of BxPC-3, MIA PaCa-2, and Capan-2 cells and slow tumor growth in the BxPC-3 xenograft model[274]. Resibufogenin, a natural product extracted from toad venom, has been found to upregulate RIPK3 to phosphorylate MLKL and produce ROS, inducing necroptosis to inhibit the proliferation and migration of HCT116 and SW480 cells and slow tumor progression and metastasis in SW480 xenograft model[275]. Similarly, (±)gossypol, natural isomers extracted from cottonseed, has been reported to upregulate the phosphorylation of RIPK3, inducing necroptosis and exerting compelling antiproliferative activity with an IC_{50} of 1.7 μmol/L in SCL-1 cutaneous squamous cell carcinoma cells[276]. Moreover, compound **38**, a pleuromutilin derivative has been identified as a novel necroptosis inducer that produced ROS and upregulated the phosphorylation of RIPK3, reducing the viability of A375 and B16F10 cells with IC_{50} values of 1.669 and 0.746 μmol/L, respectively, and effectively inhibited melanoma cells invasion; and, compound **38** also has been identified as an orally bioavailable anticancer compound that slowed tumor growth in the A375 xenograft and B16F10 syngeneic models with low toxicity[277]. Apurinic/apyrimidinic endonuclease 1 (APE1), a critical enzyme in DNA repair, is often expressed in abnormally elevated levels in multiple cancers and has been regarded as a promising cancer biomarker[278,279]. Recently, NO.0449-0145 has been identified as a novel APE1 inhibitor, which upregulated the phosphorylation of RIPK3 and MLKL to induce necroptosis, exerting compelling antiproliferative activity with an IC_{50} of 0.1068 μmol/L in A549 cells and slowing tumor progression in the NCI-H460 xenograft model[279]. MG132 and bortezomib are both proteasome inhibitors that activate RIPK3 and MLKL to induce necroptosis, inhibiting leukemia cell proliferation[280]. Arctigenin, a lignan found in certain plants of the Asteraceae, has been reported to produce ROS and upregulate the phosphorylation of RIPK3 and MLKL to induce necroptosis in PC-3 and PC-3AcT cells[281]. In addition, tanshinol A belongs to a tanshinone extracted from *S. miltiorrhiza* Bunge, which has been reported to produce ROS to upregulate the phosphorylation of MLKL, induce necroptosis and reduce the viability of A549 and H1299 cells[282]. 673A, a pan-ALDH1A inhibitor, has been found to upregulate PGAM5 to induce MLKL translocation to cell membranes, causing OV stem cell necroptosis and enhancing chemotherapy effectiveness[283]. Gallic acid has been reported to induce MLKL-mediated necroptosis in HeLa, H446, and SH-SY5Y cells[233]. Furthermore, emodin is often involved in TCMs, which has been reported to produce ROS to activate JNK, upregulating the phosphorylation of RIPK1 and MLKL, inducing necroptosis and exerting antiproliferative activity with IC_{50} values of 30.82 and 57.14 μmol/L in OS-RC-2 and 786-0 cells, respectively[284]. Similarly, Prunetin, a commonly *O*-methylated flavonoid that is often involved in plants, has been reported to produce ROS to activate JNK, upregulating the phosphorylation of RIPK3 and MLKL to induce necroptosis and inhibit AGS cell proliferation[285]. Additionally, kuguaglycoside C is a triterpene glycoside extracted from *Momordica charantia*, which has been reported to upregulate necroptosis-related regulators TRADD, AIF, and DFF45, reducing the viability of IMR-32 cells with an IC_{50} of 12.6 μmol/L[286].

Of note, there are some compounds that induce both apoptosis and necroptosis, especially in the case of low caspase activity, allowing for the induction of necroptosis as an improvement over apoptosis for therapy. For instance, the classic FDA-approved anticancer agent sorafenib has been reported to induce RIPK1-mediated necroptosis in MM cells when caspase activity is low[287]. And, the SMAC mimetic compound birinapant has been reported to induce RIPK1-mediated necroptosis in ALL cells, which effectively addressed the resistance of apoptosis after long-term treatment of ALL cells through compensatory action[288]. Similarly, SBP-0636457 has been identified as a novel SMAC mimetic compound, which upregulated the TNF-α, RIPK1, and MLKL when combined with the classical chemotherapy drug doxorubicin under the condition of apoptosis blockage, inducing necroptosis in MCF-7, MDA-MB-231, MDA-MB-453, and Hs578T cells[289].

Furthermore, there are several studies using conventional RCD inhibitors have focused on elucidating the compound-induced subroutines rather than thoroughly exploring the mechanisms. For instance, progenin III, a natural steroidal saponin extracted from Arecaceae tree fruits, has been found to produce ROS to induce necroptosis and weak autophagy, playing a stable antiproliferation role in a variety of cancer cells[290]. β-Lapachone, a natural naphthoquinone extracted from the lapacho tree bark, has been found to produce ROS to induce RIPK1-mediated necroptosis in SK-Hep1 cells[291]. Moreover, LGH00168, a CHOP activator, has been found to produce ROS to induce RIPK1-mediated necroptosis in A549 cells, exerting profound antitumor efficacy *in vitro* and *in vivo*[292]. ZZW-115 is a derivative of the classical antipsychotic agent trifluoperazine, also identified as a NUPR1 inhibitor, inducing necroptosis to show excellent antitumor activities in PAAD and HCC[293,294]. MCC1019 is a PLK1 inhibitor, which has been reported to induce necroptosis, showing cancer therapeutic potential *in vitro* and *in vivo*[295]. Similarly, BI 2536 is also a PLK1 inhibitor, which induced necroptosis in LNCaP-AI cells[296]. In addition, chlorido[4-carboxy-1,2-disalicylideneamino benzene]iron(III) derivatives have been reported to not only induce ferroptosis but also induce necroptosis to reduce the viability of HL-60 cells[243]. Similarly, chlorido[4-propoxy carbonyl-*N*,*N*′-bis(salicylidene)-1,2-phenylenediamine]cobalt(III) and chlorido[4-butoxycarbonyl-*N*,*N*′-bis(salicylidene)-1,2-phen ylenediamine]cobalt(III) have been found to induce necroptosis in A2780 and HL-60 cells (Supporting Information Table S3)[297]. At present, most compounds have been found to regulate necroptosis by directly or indirectly acting on RIPK1, RIPK3, and MLKL. Especially in the case of tumor apoptosis tolerance, compounds that induce necroptosis can re-sensitize tumors to death, which provides an effective way to overcome drug resistance. Therefore, optimizing the existing scaffolds or discovering novel drugs that target necroptosis has promising prospects for cancer therapy.

2.4. *Targeting pyroptosis, alkaliptosis, and oxeiptosis with small-molecule compounds in cancer*

2.4.1. *The key signaling pathways of pyroptosis, alkaliptosis, and oxeiptosis*

Pyroptosis is triggered by the cleavage of gasdermin D (GSDMD) by caspase family proteins, resulting in the formation of multiple pores on the cellular membrane (Fig. 5A)[298,299]. There are two main pathways for pyroptosis, one relies on caspase-1, known as the classical pathway, while the other is independent of caspase-1[35,300]. The activation of the inflammasome, a multiprotein complex mainly consisting of sensor proteins (from the AIM2-like receptors or Nod-like receptors families), adaptor protein ASC (apoptosis-associated speck-like protein containing CARD) and

effector protein procaspase-1, initiates the classical pathway of pyroptosis[4,248]. Depending on different sensors, inflammasomes can be categorized into NLRP1, NLRP3, NLRC4, NLRP6, CARD8, AIM2, and Pyrin inflammasomes[4,299,301]. When cells are stimulated by external signals such as pathogens, these sensors recognize the signals and initiate the assembly of inflammasomes. Subsequently, under mediation by ASC, they bind with procaspase-1 to complete assembly and activation of inflammasomes[4]. Activated inflammasomes then activate procaspase-1 to cleave it. Activated caspase-1 converts pro-interleukin (IL) 18 and pro-IL-1β into IL-18 and IL-1β, respectively, releasing them extracellularly to amplify inflammatory responses; simultaneously it cleaves GSDMD protein into active N-terminal and C-terminal fragments where its N-terminal fragment promotes pore formation leading to cell death[35,300]. The non-caspase-1-dependent pyroptosis is initiated by lipopolysaccharide (LPS), whereby the CARD domains of caspase-4/5 (human) or caspase-11 (mouse) directly bind to LPS and become activated. Upon activation, caspase-4/5/11 cleaves GSDMD protein into active N-terminal and C-terminal fragments, with the former fragment mediating cell death[248,301]. Additionally, membrane pores formed by GSDMD result in K^+ efflux, activate NLRP3 inflammasomes, trigger caspase-1 activation, and amplify its inflammatory response[299]. Recent studies have demonstrated that ROS can enhance GSDMD activity through oxidative modification of cysteine 192 (C192)[302]. Moreover, it has been discovered that the N-terminal segment of GSDMD functions as a negative feedback regulator that controls the activation of inflammasomes[303]. Concurrently, studies have demonstrated the significant function of NLRP11 as a constituent of NLRP3 inflammasomes in human macrophages[304].

In addition, recent investigations have unveiled the involvement of additional members within the caspase family in the regulation of the pyroptosis signaling pathway. For instance, when apoptosis and necroptosis are inhibited, caspase-8 activity

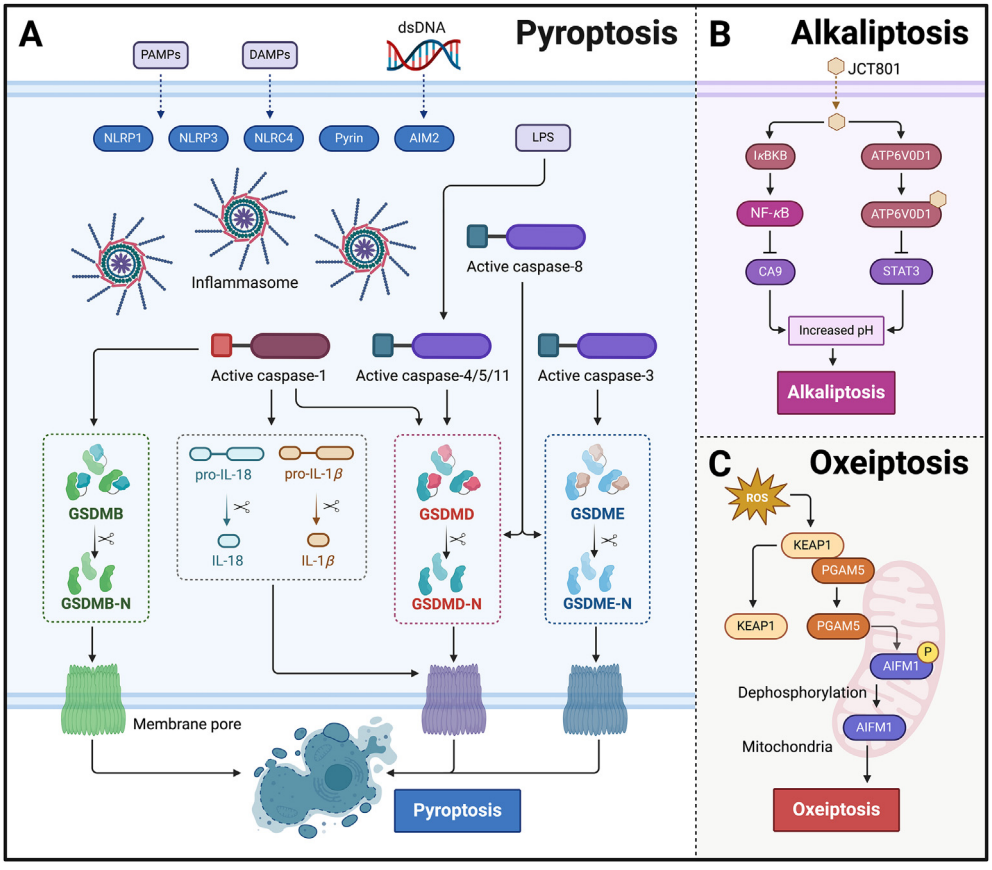

Figure 5 The key signaling pathways of pyroptosis, alkaliptosis, and oxeiptosis. (A) When external signals stimulate cells, the inflammasome (*e.g.*, NLRP1, NLRP3, NLRC4, Pyrin, and AIM2) starts to assemble and activate caspase-1. Then activated caspase-1 converts pro-IL-18 and pro-IL-1β into IL-18 and IL-1β, respectively releasing them extracellularly to amplify inflammatory responses; simultaneously it cleaves GSDMD into active N-terminal and C-terminal fragments where its N-terminal fragment promotes pore formation leading to cell death. The non-caspase-1-dependent pyroptosis is initiated by LPS, whereby the CARD domains of caspase-4/5 (human) or caspase-11 (mouse) directly bind to LPS and become activated. Upon activation, caspase-4/5/11 cleaves the GSDMD into active N-terminal and C-terminal fragments, inducing cell death. Similarly, active caspase-3 and caspase-8 cleave GSDMD/E to induce pyroptosis. (B) Alkaliptosis is initiated by lysosomal pH dysfunction, small molecule JTC801 activates NF-κB to downregulate CA9 and also mediates the interaction between ATP6V0D1 and STAT3, leading to increased pH to trigger cell death. (C) Oxeiptosis is mainly mediated by the KEAP1−PGAM5−AIFM1 axis to induce protein oxidation and DNA damage to trigger cell death. High concentrations of ROS cause dissociation between PGAM5 and KEAP1 followed by detachment of PGAM5 from the outer membrane of mitochondria. The liberated PGAM5 then translocates into mitochondria to dephosphorylate AIFM1, ultimately leading to oxeiptosis.

can govern the cellular transition from cell death to pyroptosis[305]. Moreover, caspase-8 can modulate the activation of atypical inflammasomes through the autophagy−cathepsin-B axis[305]. Similarly, caspase-3 is significant in the pyroptosis pathway[306].

Moreover, GSDMB, GSDMC, and GSDME have also been shown to mediate pyroptosis[300,307−309]. It is worth noting that alternative splicing has a very fine regulation of the pore-forming activity of gasdermin family members. For example, the crystal structure of GSDMB pores recently resolved by cryoelectron microscopy showed that the interdomain linker regulated by alternative splicing in GSDMB is the regulator of GSDMB pore formation[307]. The GSDMB splice isoform with a typical interdomain linker showed normal pyroptosis activity, whereas the other isoforms showed reduced or no pyroptosis activity[310]. This work also clarified the misconception that GSDMB has no pyroptosis activity because previous works used a variant of GSDMB generated by non-classical alternative splicing, whose insertion sequence in front of exon 6 disrupts the pore-forming ability of the N-terminal domain of GSDMB[311,312]. Finally, other key regulators are also essential for the pyroptosis pathway. For instance, ubiquitin-specific protease (USP) 48, a deubiquitinating enzyme, has been demonstrated to interact with GSDME and remove ubiquitin chains at K120 and K189 sites, thereby enhancing the stability of GSDME and promoting pyroptosis[313]. Similarly, USP18 has been found to regulate pyroptosis by modulating tumor cell necrosis-related proteins like polo-like kinase 2[314]. Additionally, studies have indicated that TRK-fused gene and TRAF3-mediated ULK1 ubiquitination exert significant regulatory effects on LPS-induced pyroptosis[315]. Moreover, several non-coding RNAs including miR-223-3p, LINC00023, LINC00969, miR-1184, and miR-28a-5p have also been implicated in the regulation of the pyroptosis pathway[316−319].

Alkaliptosis is driven by intracellular alkalization and pH-dependent processes (Fig. 5B)[4,320]. The concept of alkaliptosis was proposed in 2018 when the authors conducted a screening of a small molecule library targeting G protein-coupled receptors and identified JTC801, which exhibited potent cytotoxic activity against human PAAD cells. Though blocking of these pathways did not alter JTC801-induced cell death, the mechanism behind JTC801-induced cell death was different from recognized types of RCD, such as apoptosis, ferroptosis, or necroptosis. Rather, JTC801-induced cell death may be avoided by inhibiting intracellular alkalization in an acidic environment[23]. Recent research has shown that JTC801 mediates the interaction between ATP6V0D1 and STAT3, hence inducing alkaliptosis in PAAD cells[321]. It is currently believed that the downregulation of carbonic anhydrase 9, dependent on the IκB−NF-κB pathway, can trigger alkaliptosis; the specific mechanism, however, still requires further elucidation[23]. Furthermore, additional study is needed to explore the role played by alkaliptosis in human diseases.

Oxeiptosis is a caspase-independent form of RCD that is sensitive to ROS and was first conceptualized in 2018 (Fig. 5C)[322]. This process is mediated by the KEAP1−PGAM5−AIFM1 pathway[24]. Oxeiptosis can be triggered by ROS, which may originate from endogenous sources such as mitochondrial oxidative phosphorylation, redox reactions within peroxisomes and lysosomes, as well as exogenous sources like H_2O_2 and O_3[24,323]. ROS further induces protein oxidation, DNA damage, and ultimately cell death. When intracellular ROS levels are elevated, they are sensed by the ROS-sensing protein KEAP1 (an E3 ubiquitin ligase), initiating oxeiptosis[324]. Low concentrations of ROS lead to cellular oxidative stress that promotes the dissociation of KEAP1 from NRF2 and subsequent binding with PGAM5[24,323]. The released NRF2 translocates into the nucleus, where it forms complexes with antioxidant response elements to initiate the transcription of antioxidant genes responsible for eliminating excessive ROS[324]. Conversely, high concentrations of ROS cause dissociation between PGAM5 and KEAP1 followed by detachment of PGAM5 from the outer membrane of mitochondria[4]. The liberated PGAM5 then translocates into mitochondria to dephosphorylate AIFM1, ultimately leading to oxeiptosis[24,323]. However, further research is warranted to elucidate specific mechanisms underlying oxeiptosis including the interaction between PGAM5 and AIFM1 as well as how dephosphorylated AIFM1 induces oxeiptosis in cells. Additionally, studies have demonstrated that OTUD1 interacts with KEAP1 through its N-terminal intrinsically disordered region containing ETGE motifs thereby participating in KEAP-mediated oxeiptosis regulation[325]. Furthermore, oxeiptosis-related long non-coding RNAs (lncRNAs) are potentially associated with prognosis in uterine corpus endometrial carcinoma[326].

2.4.2. *Small-molecule compounds targeting pyroptosis, alkaliptosis and oxeiptosis*

Notably, numerous compounds have been found to induce pyroptosis *via* the classical approach, namely activating caspase-1 to cleave GSDMD in various cancer cells. For instance, cisplatin, a classical chemotherapy drug, has been reported to upregulate lncRNA MEG1 to activate NLRP3 and caspase-1, cleaving GSDMD to induce pyroptosis and exert antiproliferative activity with an IC_{50} of 9.952 μmol/L in MDA-MB-231 cells, slowing tumor progression in the MDA-MB-231 xenograft model, and inhibit invasion *in vitro* and *in vivo*[327]. Sorafenib is also a classical chemotherapy drug that has been found to activate caspase-1 to induce pyroptosis in macrophages, enhancing anti-tumor immunity *via* natural killer cells in HCC[328]. 2-(Anaphthoyl)ethyltrimethylammonium iodide is a choline acetylcholine transferase inhibitor that has been reported to activate caspase-1 to cleave GSDMD, inducing pyroptosis to reduce the viability of Ho8910, Ho8910PM and A2780 cells, and slowing tumor growth in the SKOV3 xenograft model[329]. Chidamide is a histone deacetylase inhibitor that has been found to activate caspase-1 to cleave GSDMD, inducing pyroptosis in TU212 and AMC-HN-8 cells, and slowing tumor growth *in vivo*[224]. Flubendazole is a classic repurposing non-oncology azole compound available for cancer treatment, which has been reported to activate NF-κB and NLRP3, inducing caspase-1 to cleave GSDMD, triggering pyroptosis and inhibiting proliferation with IC_{50} values of 0.1701 and 0.2243 μmol/L in U87MG and U251 cells, and slowing tumor growth in the U87MG xenograft model[330]. D089 is an MYC G4-quadruplex stabilizer that has been reported to activate the NLRP3 inflammasome and caspase-1 to cleave GSDMD with the increased HMGB1 and IL-1β, inducing pyroptosis to inhibit L363 cell proliferation[331]. Similarly, JQ1 is a BRD4 inhibitor that has been found to activate the NLRP3 inflammasome and caspase-1 to cleave GSDMD with the increased IL-1β, inducing pyroptosis to inhibit ACHN cell proliferation[332]. Simvastatin is a classic cholesterol-lowering drug that has been found to activate NLRP3 to induce caspase-1-mediated pyroptosis in H1299 and A549 cells, which exhibit antitumor activity *in vitro* and *in vivo*[333]. And, simvastatin has also been reported to activate caspase-3 to cleave GSDME, inducing pyroptosis and exerting antiproliferative activity with

an IC_{50} of 4.623 μmol/L in MGC-803 cells, and slowing tumor growth in the MGC-803 xenograft model[334]. Moreover, ValboroPro is a DPP8/9 inhibitor that has been found to activate Nlrp1b inflammasome, triggering caspase-1-mediated pyroptosis in AML cells, and exerting antitumor activity *in vitro* and *in vivo*[335,336]. DHA, an essential polyunsaturated fatty acid that induces autophagy-dependent cell death in MCF-7 cells, has been reported to activate NF-κB, caspase-1, and GSDMD with the increased IL-1β and HMGB1, inducing pyroptosis to inhibit proliferation in MDA-MB-231 cells[337]. No.0449-0145, a novel APE1 inhibitor, has been found to activate caspase-4 and GSDMD with the increased IL-1β, inducing pyroptosis to inhibit proliferation in A549 and NCI-H460 cells and slowing tumor growth in the NCI-H460 xenograft model[279]. Furthermore, cucurbitacin B, a natural product existing in Cucurbitaceae plants, has been reported to activate the NLRP3 inflammasome and produce ROS with the accumulation of Tom20 and Ca^{2+}, increasing the cleaved GSDMD to induce pyroptosis, which reducing the viability of A549 cells and A549 xenograft model[338]. PPVI has been reported to produce ROS to activate NF-κB, activating the NLRP3 inflammasome and caspase-1 to cleave GSDMD, inducing pyroptosis in A549 and H1299 cells[339]. Similarly, alpinumisoflavone, a natural product extracted from derriseriocarpa, has been reported to activate the NLRP3 inflammasome and caspase-1 to cleave GSDMD with the increased IL-18 and IL-1β, inducing pyroptosis to inhibit proliferation and invasion in SMMC 7721 and Huh-7 cells, and slowing tumor growth *in vivo*[340]. Mallotucin D, a natural diterpene extracted from *Croton crassifolius*, has been reported to produce ROS and activate the NLRP3 inflammasome and caspase-1 to cleave GSDMD with the increased IL-1β, inducing pyroptosis to inhibit proliferation with an IC_{50} of 26.9 ± 0.6 μmol/L in HepG2 cells, and slowing tumor growth in the HepG2 xenograft model[341]. Sophflarine A, a novel matrine-derived alkaloid from *S. flavescens*, has been reported to activate the NLRP3 inflammasome and caspase-1 to cleave GSDMD, inducing pyroptosis to inhibit proliferation with IC_{50} values of 11.3 ± 0.8 and 11.5 ± 0.6 μmol/L in A549 and H820 cells, and slowing tumor growth in the A549 orthotopic xenograft model[94]. Secoisolariciresinol diglucoside, a lignan extracted from flaxseed, has been reported to produce ROS and activate PI3K to upregulate BAX, activating caspase-1 to cleave GSDMD, inducing pyroptosis to reduce the viability of HCT116 cells and HCT116 xenograft model[342]. Wedelolactone, a natural coumarin purified from *Eclipta prostrata*, has been reported to produce ROS and activate caspase-1 to cleave GSDMD and GSDME, inducing pyroptosis to inhibit proliferation in Y79 and Weri-Rb human retinoblastoma (Rb) cells, and slowing tumor growth in the Y79 xenograft model[343]. Notably, in Rb, GSDME also has been found to improve sensitivity to chemotherapy drugs *via* pyroptosis induction[344]. Nobiletin, a natural product extracted from citrus fruits, has been reported to produce ROS to induce GSDMD/GSDME pyroptosis with the increased IL-1β, exerting antiproliferative activity with IC_{50} values of 35.31 and 34.85 μmol/L in A2780 and OVCAR3 cells[123].

Additionally, numerous compounds have been discovered to induce pyroptosis *via* several emerging approaches, the most common of which is to activate caspase-3 to cleave GSDME, inducing pyroptosis to exert antitumor efficacy. For instance, based on an extensive study of the classical chemotherapy drugs, topotecan, etoposide, cisplatin and CPT-11 have been found to induce pyroptosis in GSDME-positive SH-SY5Y cells; and doxorubicin, actinomycin-D, bleomycin and topotecan have been reported to activate caspase-3 to cleave GSDME, inducing pyroptosis in NCI-H522 cells[345]. Similarly, MEK inhibitor trametinib, EGFR inhibitor erlotinib, and ALK inhibitor ceritinib have been found to activate caspase-3 to cleave GSDME, upregulating the cleaved caspase-3 and N-GSDME to induce pyroptosis in A549 ($KRAS^{G12S}$), PC9 ($EGFR^{E746\text{-}A750\ del}$) and NCI-H3122 (*EML4-ALK* fusion gene) cells, respectively[346]. BRAF inhibitors combined with MEK inhibitors have been found to increase cleaved GSDME and HMGB1, inducing pyroptosis to reduce the viability of *BRAF* mutant melanoma cells[347]. Classical proteasomal inhibitors MG132 and bortezomib have been reported to block the interaction between BCL-2 and BAX, upregulating BAX to activate caspase-3, -6, -7, and -9 to cleave GSDME, and the increased N-GSDME also feedback activating caspase-3 and -9, inducing pyroptosis in RPMI-8226 cells[348]. Moreover, cisplatin also has been reported to activate calpain-1 and -2 to activate caspase-9 and -3, cleaving GSDME to induce pyroptosis and exert antiproliferative activity with IC_{50} values of 10.85 and 11.95 μmol/L in KYSE30 and KYSE510 human esophageal squamous cell carcinoma (ESCC) cells, respectively[349]. And, both cisplatin and the classical chemotherapy drug paclitaxel could induce pyroptosis *via* activating caspase-3 to cleave GSDME in A549 cells; especially, compared to paclitaxel, cisplatin induced a higher level of pyroptosis[350]. Similarly, navitoclax, a classical chemotherapy drug, has been reported to induce pyroptosis *via* activating caspase-3, -7, and -9 to cleave GSDME in HCT116 cells[351]. In addition, lobaplatin is a classical chemotherapy drug that has been reported to produce ROS and activate JNK to upregulate BAX, activating caspase-3 and -9 to induce GSDME-mediated pyroptosis in HT-29 and HCT116 cells[352]. Lobaplatin also has been reported to inhibit cIAP1/2 to produce ROS, activating caspase-3 to cleave GSDME, inducing pyroptosis to inhibit proliferation in CNE-1, S26, HONE-1, SUNE-1, and CNE-2 cells, and slowing tumor growth in the CNE-1 and S26 xenograft model[353]. Tetraarsenic hexoxide is a classical chemotherapy drug that has been reported to inhibit STAT3 to produce ROS and activate caspase-3 to cleave GSDME, inducing pyroptosis to inhibit proliferation in multiple TNBC cells, and slowing tumor growth in the 4T1 syngeneic mouse model[354]. 5-FU, a classical chemotherapy drug, has been reported to induce pyroptosis *via* activating caspase-3 to cleave GSDME and inhibit proliferation in SGC-7901 and MKN-45 cells[355]. Metformin is a classic diabetes drug that has been reported to activate the AMPK/SIRT1/NF-κB pathway to upregulate BAX, activating caspase-3 to cleave GSDME, and inducing pyroptosis in HepG2, MCF-7, HCT-15 and HT-29 cells[356]. And, in ESCC, metformin has been reported to upregulate miR-497 while suppressing PELP1, inducing GSDMD-mediated pyroptosis to inhibit proliferation *in vitro* and *in vivo*[357]. Triclabendazole is a classic repurposing non-oncology azole compound available for cancer treatment, which has been found to produce ROS and activate caspase-3 to cleave GSDME, inducing pyroptosis in MCF-7 and MDA-MB-231 cells and slowing tumor growth in the MDA-MB-231 xenograft model[358]. Moreover, based on CRC cancer tissue-originated spheroids screening, BI 2536 and (*S*)-(+)-camptothecin have been found to activate caspase-3 to cleave GSDME, inducing pyroptosis and exert antitumor activity *in vitro* and *in vivo*[359]. And, BI 2536 has also been reported to activate caspase-3 to cleave GSDME, inducing pyroptosis and exerting excellent antiproliferative activity with an IC_{50} of 0.439 μmol/L in A2780 cells[360]. When combined with cisplatin, BI 2536 also induced pyroptosis in ESCC cells *via* activating caspase-3 to cleave GSDME and enhanced the antitumor efficacy of cisplatin[361]. Similarly, STAT3β is a splice variant of STAT3, which

also increased ROS to activate caspase-3 and GSDME during the cisplatin treatment in ESCC cells, inducing pyroptosis to improve sensitivity to cisplatin[362]. GW4064, an FXR agonist, has been found to upregulate BAX to activate caspase-3, cleaving GSDME to induce pyroptosis, which improved CRC cell sensitivity to oxaliplatin[363]. In addition, liproxstatin-1 has been found to activate caspase-3 to cleave GSDME, inducing pyroptosis and exerting compelling anti-proliferative activity with an IC_{50} of 11.4 μmol/L in K562 cells[122]. AT7519, a CDK inhibitor that has been found to activate caspase-3 to cleave GSDME, inducing pyroptosis to inhibit proliferation with IC_{50} values of 0.246 and 0.2218 μmol/L in U251 and U87MG cells, and slowing tumor growth in the U87MG orthotopic xenograft model[364]. Raptinal, a caspase-3 activator that has been found to activate caspase-3 to cleave GSDME with the increased HMGB1 and IL-1α or IL-1β, inducing pyroptosis to inhibit BRAFi and MEKi-resistant melanoma cell proliferation *in vitro* and *in vivo*[365]. C-02, a degrader of critical rate-limiting enzyme hexokinase 2 in glycolysis, has been reported to produce ROS to release cytochrome c and activate caspase-3 to cleave GSDME, inducing pyroptosis to exert compelling antiproliferative activity with an IC_{50} of 5.08 ± 1.54 μmol/L in 4T1 cells, and slowing tumor growth in the 4T1 mouse model[366]. Moreover, bexarotene is an FDA-approved agent for cutaneous T-cell lymphoma, which has been found to activate caspase-4 and GSDME to induce pyroptosis to inhibit proliferation in ES2 cells[367]. α-Ketoglutarate, a metabolite that has been reported to produce ROS to oxidize DR6 and activate caspase-8 to cleave GSDMC, inducing pyroptosis and inhibiting HeLa cell proliferation *in vitro* and *in vivo*[309]. Furthermore, alantolactone, a natural sesquiterpene lactone extracted from *Inula helenium* L., has been reported to produce ROS and upregulate BAX to activate caspase-3, cleaving GSDME and upregulating the cleaved caspase-3 and N-GSDME to induce pyroptosis, exerting antiproliferative activity with IC_{50} values of 7.886 and 4.505 μmol/L in 8505C and KHM-5M human anaplastic thyroid cancer (ATC) cells, and slowing tumor growth in the 8505C xenograft model[368]. Dihydroartemisinin has been found to activate caspase-3 and -8 to cleave GSDME, upregulating N-GSDME to induce pyroptosis in Eca-109 and Ec9706 cells and inhibit tumor proliferation *in vitro* and *in vivo*[369]. Moreover, dihydroartemisinin also upregulated AIM2 to activate caspase-3 to cleave GSDME, increasing N-GSDME to induce pyroptosis in MCF-7 and MDA-MB-231 cells to exert antitumor activity *in vitro* and *in vivo*[370]. Neobractatin, a natural product extracted from *Garcinia bracteate*, has been found to produce ROS and activate caspase-3 to cleave GSDME, upregulating N-GSDME to induce pyroptosis and inhibit proliferation in KYSE150, KYSE450, and Eca-109 cells and slowing tumor growth in the KYSE150 xenograft model[371]. Triptolide has been reported to inhibit HK-II to activate BAX and Bad, then activate caspase-3 to cleave GSDME, inducing pyroptosis to reduce the viability of HK1 and FaDu cells[372]. Gambogic acid, a characteristic flavonoid from the resin of *Garcinia hanburyi*, has been found to activate caspase-3 to cleave GSDME, inducing pyroptosis in HCT116 and CT26 cells, and slowing tumor growth in the CT26 syngeneic model[373]. Neobavaisoflavone, a natural product extracted from *Psoralea* plants, has been reported to produce ROS with the accumulation of Tom20, activating BAX and caspase-3 to cleave GSDME, inducing pyroptosis to reduce the viability of HCCLM3 and HepG2 cells with IC_{50} values of 53.49 and 48.12 μmol/L and slow tumor growth *in vivo*[374]. Aloe-emodin, a natural anthraquinone identified from *Rheum palmatum* L., has been reported to activate BAX, caspase-9, and caspase-3 to cleave GSDME, inducing pyroptosis to inhibit proliferation and migration in HeLa cells[375]. Osthole has been found to induce GSDME-mediated pyroptosis in OVCAR3 and A2780 cells[124]. Miltirone, a natural product extracted from *S. miltiorrhiza* Bunge, has been reported to produce ROS to inhibit the MEK−ERK1/2 axis, activating BAX, caspase-9, and -3 to cleave GSDME, inducing pyroptosis to reduce the viability of HepG2 and Hepa1-6 cells[376]. Moreover, chalcone is a kind of well-known natural product with antitumor activities, whose derivatives were synthesized and evaluated for activity against NSCLC cells; the results showed that compound **8** exerted reliable antiproliferative activity with IC_{50} values of 2.3, 3.2 and 5.7 μmol/L in NCI-H460, A549, and H1975 cells *via* produce ROS to induce caspase-3-mediated pyroptosis[377].

Hitherto, there are several compounds have been reported to induce alkaliptosis, or oxeiptosis to exert antitumor activity. For instance, JCT801 is a classical analgesic agent that has been reported to activate NF-κB to downregulate carbonic anhydrase CA9, inducing alkaliptosis to inhibit proliferation in multiple PAAD cells, and slowing tumor growth in the PANC-1 xenograft model[23]. Then, further mechanism exploration found that JCT801 directly targeted ATP6V0D1, and the increased ATP6V0D1 suppressed STAT3, leading to lysosomal pH dysfunction to induce alkaliptosis in PAAD cells to exert antitumor activity *in vitro* and *in vivo*[321]. Moreover, Venetoclax, the classic FDA-approved BCL-2 inhibitor for leukemia therapy, which resistance often occurs due to the increased NF-κB; therefore, JCT801 induced NF-κB-mediated CA9 downregulation leading to increased pH and alkaliptosis, alleviating venetoclax resistance in AML cells[378]. In addition, auriculasin has been reported to produce ROS and activate KEAP1 to dephosphorylate AIFM1, inducing oxeiptosis and inhibiting proliferation and migration in HCT116 and SW480 cells (Supporting Information Table S4)[223]. At present, small-molecule compounds that target pyroptosis are currently being developed, and they can be used to treat a range of cancers. The two most popular ways are: to activate the NLRP3 inflammasome and caspase-1 to cleave GSDMD and activate caspase-3 to cleave GSDME. Targeting pyroptosis is a prominent cancer therapy. Furthermore, the mechanism of alkaliptosis and oxeiptosis remains poorly understood, necessitating additional study.

2.5. *Targeting parthanatos, MPT-driven necrosis, entotic cell death, and NETotic cell death with small-molecule compounds in cancer*

2.5.1. *The key signaling pathways of parthanatos, MPT-driven necrosis, entotic cell death, and NETotic cell death*

Parthanatos differs from apoptosis and is caused by abnormal DNA damage-induced PARP-1 activation (Fig. 6A)[379,380]. Unique features of parthanatos include excessive activation of PARP-1, synthesis and accumulation of PAR, mitochondrial depolarization, and AIF nuclear translocation[244,380,381]. Under normal physiological conditions, moderate activation of PARP-1 is essential for sensing and modulating stress for DNA repair[380]. However, under pathological conditions such as extensive DNA damage caused by stimuli like ROS, UV radiation, alkylating agents, or inflammation, overactivation of PARP-1 leads to caspase-independent cell death[4,380]. Excessive activation results in toxic accumulation of PAR within cells which depletes NAD^+ and ATP levels while inhibiting the activity of mitochondrial respiratory chain complex I−III enzymes leading to impaired tricarboxylic acid cycle pathway and disrupted mitochondrial energy metabolism. Additionally, it triggers the release of parthanatos-associated AIF along with MIF, ultimately resulting in chromatin condensation and large-scale DNA fragmentation[4,244,382].

MPT-driven necrosis is a type of RCD that occurs when the cellular microenvironment is disrupted due to stress or damage, such as severe oxidative stress or Ca^{2+} overload (Fig. 6B)[383,384]. It exhibits morphological characteristics of cell death. The formation of MPTP on the mitochondrial inner membrane is triggered by an excess concentration of calcium ions within cells, resulting in changes in mitochondrial permeability, ATP depletion, rupture of the outer mitochondrial membrane, and pro-apoptotic factors release, leading to either apoptosis or necrosis depending on the degree of MPTP opening[385]. MPTP is a complex composed of multiple components, including adenine nucleotide translocator, VDAC, and CypD[386–389]. Its conformation is regulated by various factors, which still require further research. Currently, CypD is believed to be a positive regulatory factor that is indispensable for MPTP[383]. The occurrence of MPT-driven necrosis results from an imbalance between the opening and closing of MPTP[383]. In addition to external injuries causing the abnormal opening of MPTP, other factors also regulate its opening; for example, low pH during ischemia inhibits the opening of MPTP[390]. Recent studies have also reported that non-traditional openings of MPTP can be regulated by mitochondrial dynamics[391].

Entotic cell death involves one cell engulfing and killing another through entosis (Fig. 6C)[20,244,392]. Morphologically distinct from other types of RCD, it contains cell-in-cell structures (CICs) formation first observed in 1956[393]. CICs can be classified as homotypic CICs occurring mainly between tumor cells or heterotypic CICs occurring mainly between tumor cells and immune cells[4,394,395]. Entotic cell death can be triggered by various factors, including abnormal proliferation, matrix deadhesion, mitotic stress, and glucose deprivation[244,394]. Once activated, similar cells are engulfed and killed *via* LC3-associated phagocytosis followed by lysosomal degradation mediated by cathepsin B[392,394]. During this process, pathways involving cellular adhesion and cytoskeletal rearrangement play important roles including actin/myosin filaments and RHOA/ROCK[4,20,396].

Etotic cell death, also known as NETosis, is driven by NETs (Fig. 6D)[4,397]. This process involves NADPH oxidase-mediated

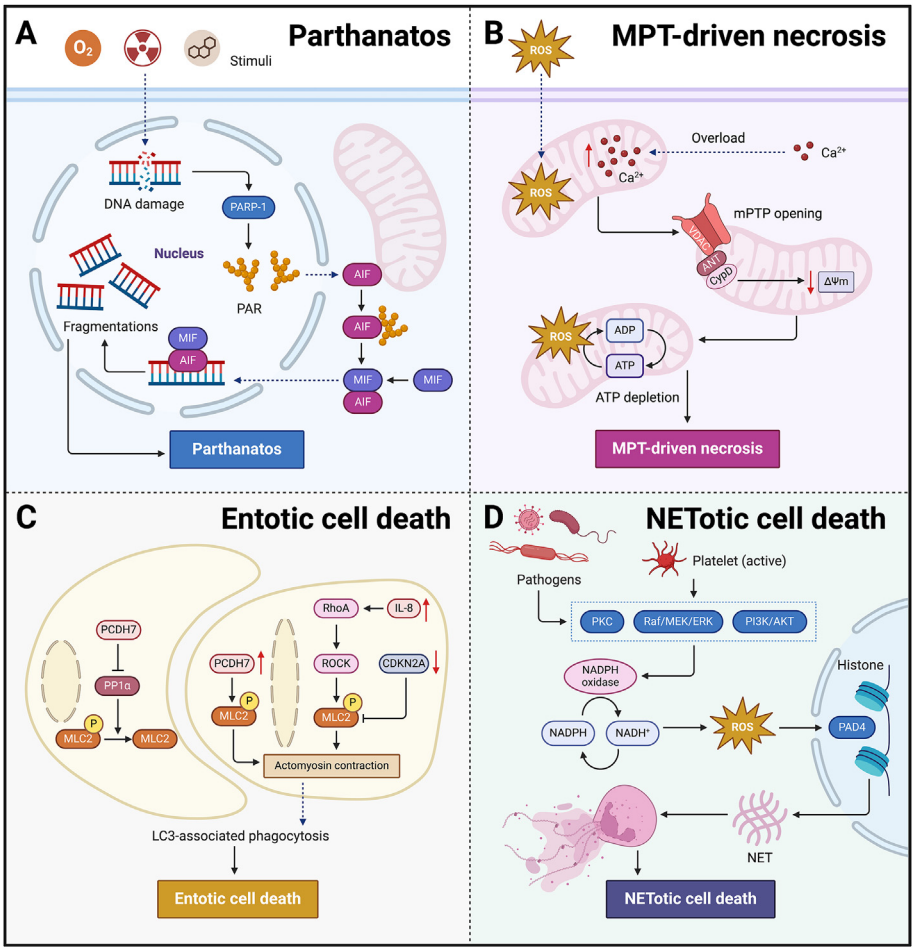

Figure 6 The key signaling pathways of parthanatos, MPT-driven necrosis, entotic cell death, and NETotic cell death. (A) Parthanatos is commonly initiated by DNA damage, abnormally activating PARP-1 and inducing AIF and MIF translocation to nuclear with the accumulation of PAR, leading to chromatin condensation and large-scale DNA fragmentation to trigger cell death. (B) MPT-driven necrosis is primarily triggered by Ca^{2+} overload, excess Ca^{2+} induces MPTP opening and CypD activation, leading to ATP depletion to trigger cell death. (C) Entotic cell death is one cell engulfing and killing another through entosis. Once activated, similar cells are engulfed and killed *via* LC3-associated phagocytosis. (D) NETosis is commonly initiated by pathogens or activated platelets, which activate PKC, Raf−MEK−ERK, and PI3K−Akt signaling pathways to produce ROS, leading to histone citrullination by peptidyl arginine deiminase. Citrullinated histone H3 alters chromatin charge and promotes its unwinding. Subsequently, the nuclear membrane and granular membrane undergo dissolution, allowing antimicrobial proteins to attach to the decondensed chromatin forming a mesh-like structure NET that is eventually released into the extracellular space.

ROS production and histone citrullination[397]. NETs are extracellular DNA-protein structures released in response to infection or injury with various biological functions, including resistance against pathogen invasion, promotion of thrombosis, and tumor metastasis[397,398]. The dynamic process of NETosis depends on multiple signals and steps where Raf-1, MEK, and ERK play crucial roles[244,398]. NETosis can be induced by various factors, including pathogens, activated platelets, and chemotactic factors[399]. These inducers activate protein kinase C, which in turn activates the Raf/MEK/ERK signaling pathway to ROS production[397,398]. This leads to histone citrullination by peptidyl arginine deiminase 4. Citrullinated histone H3 alters chromatin charge and promotes its unwinding. Subsequently, the nuclear membrane and granular membrane undergo dissolution, allowing antimicrobial proteins to attach to the decondensed chromatin forming a mesh-like structure that is eventually released into the extracellular space[4]. Additionally, Toll-like receptors and complement C3 protein activation can also trigger NETosis; however, their specific mechanisms remain unclear[244,397,400].

2.5.2. *Small-molecule compounds targeting parthanatos, MPT-driven necrosis, entotic cell death, and NETotic cell death*

Numerous compounds have been discovered to abnormally activate the essential parthanatos regulator PARP-1, inducing parthanatos to exert antitumor efficacy. For instance, the *N*-methyl-*N*′-nitro-*N*′-nitrosoguanidine, an alkylating agent, has been reported to produce ROS, leading to DNA damage to abnormally activate PARP-1, triggering parthanotos to inhibit proliferation in HeLa and HCT116 cells[401]. Moreover, nifuroxazide is a nitrofuran agent that has been identified as a novel E-26 transformation-specific-related gene (ERG) inhibitor, which blocked the interaction of ERG with PARP-1, abnormally activating PARP-1 to induce parthanotos with the accumulation of AIF, exerting reliable antiproliferative activity with an IC_{50} of 2.56 ± 0.08 μmol/L in *TMPRSS2:ERG*-positive VCaP cells and slowing tumor growth in the VCaP xenograft model[402]. ZINC253504760 is a MEK inhibitor that has been reported to induce DNA damage and AIF translocation to nuclear with the accumulation of PARP-1 and PAR, inducing parthanotos and inhibiting proliferation with an IC_{50} of 0.022 ± 0.002 μmol/L in CCRF-CEM cells[403]. BAY87-2243 is a respiratory chain inhibitor that activated PARP-1 and AIFM1 combined with α-ketoglutarate, inducing parthanotos in NCI-H460 cells[404]. In addition, fumonisin B1 is a metabolite produced by *Fusarium* spp., which has been reported to induce DNA damage to abnormally activate PARP-1 and induce AIF translocation to nuclear with the accumulation of PAR, inducing parthanotos in SH-SY5Y cells[405]. Brachydin A, a flavonoid extracted from *Fridericia platyphylla*, has been reported to activate PARP-1 to induce parthanotos, inhibiting proliferation and invasion in DU145 3D cell cultures[406]. Deoxypodophyllotoxin, a natural product extracted from *Anthriscus sylvestris*, has been reported to produce ROS to abnormally activate PARP-1 and induce AIF translocation to nuclear with the accumulation of PAR, inducing parthanotos and exerting compelling antiproliferative activity with IC_{50} values of 188 and 462 nmol/L in C6 and SHG-44 cells and slowing tumor growth in the C6 syngeneic model[407]. β-Lapachone has been reported to produce ROS to abnormally activate PARP-1 and induce AIF translocation to nuclear, triggering parthanotos in SK-Hep1 cells[291].

So far, only a few compounds have been reported to induce MPT-driven necrosis, entotic cell death, or NETotic cell death to exert antitumor activity. For instance, isobavachalcone is a natural flavonoid identified from *Psoralea corylifolia* Linn., which has been reported to produce ROS, leading to Ca^{2+} overload, CypD activation, MPTP opening, and mitochondrial membrane depolarization, inducing MPT-driven necrosis in 4T1 and A549 cells, and slowing tumor growth in the 4T1 syngeneic model[408]. Moreover, methylseleninic acid and ethyl analogs compounds **1** and **2** have been reported to exert compelling antiproliferative activity with IC_{50} values of 2.28, 3.31 and 1.43 μmol/L in PANC-1 cells, respectively, and inhibit proliferation in PANC-1 3D cell cultures; moreover, methylseleninic acid and compounds **1** and **2** also downregulated CDC42 and CD29 to trigger cell detachment, upregulating CTSB to induce entotic cell death in PANC-1 cells[409]. Moreover, tunicamycin is a glycosyltransferase inhibitor that has been found to induce NETotic cell death in HL-60 cells (Supporting Information Table S5)[410]. Currently, targeting parthanatos for cancer therapy is a meaningful strategy, relevant small-molecule compounds work mainly by inducing DNA damage and activating PARP-1. Moreover, targeting MPT-driven necrosis, entotic cell death, and NETotic cell death have not been studied much in cancer therapy, possibly due to their mechanisms remaining to be further explored.

2.6. *Targeting lysosome-dependent cell death with small-molecule compounds in cancer*

2.6.1. *The key signaling pathways of lysosome-dependent cell death*

Lysosome-dependent cell death is initiated by LMP, which leads to the release of hydrolytic enzymes and subsequent lysosome rupture (Fig. 7)[4,35,244]. The lysosomes are organelles enclosed by a membrane and contain diverse hydrolytic enzymes capable of breaking down cellular components, including proteins, carbohydrates, and lipids[411]. Exposure to external stimuli such as ROS triggers LMP, leading to the release of many hydrolytic enzymes and leading to lysosome-dependent cell death[412,413]. Cathepsins play a crucial role in initiating and executing lysosome-dependent cell death, depending on the environment of lysosomal membrane permeability[4]. Inhibiting the expression or activity of cathepsins can effectively reduce the occurrence of lysosome-dependent cell death. STAT3 and p53 specifically upregulate the expression of cathepsins, such as *CTSB*, *CTSL*, and *CTSD*, to promote the induction of lysosome-dependent cell death[414−416]. Lysoptosis is a recently reported pathway that depends on LMP and released cathepsin (mainly CTSL) in the absence of mSerpinb3a and SERPINB3[417]. Additionally, LAMP3 regulates lysosome-dependent cell death by inducing dysfunctioning lysosomes leading to inhibition of autophagic caspase-8 degradation resulting in lysosome-dependent cell death induction[418]. Recent studies have shown that the LCDR/hnRNP K/LAPTM5 axis is essential for regulating lysosome-dependent cell death in NSCLC[419].

2.6.2. *Small-molecule compounds targeting lysosome-dependent cell death*

Notably, there are several compounds that induce LMP to release lysosomal cathepsin, triggering lysosome-dependent cell death to exhibit antitumor activities. For instance, to explore lysosome-/mitochondria-targeting compounds with the novel scaffold, virtual screening was performed, then EDK-87 and EDK-88 were hit. EDK-87 and EDK-88 also have been identified as novel tetracyclic antileukemic compounds, which induced LMP to trigger lysosome-dependent cell death, exerting promising antiproliferative activity in multiple AML cells and slowing tumor growth in the KG1 and MonoMac1 xenograft

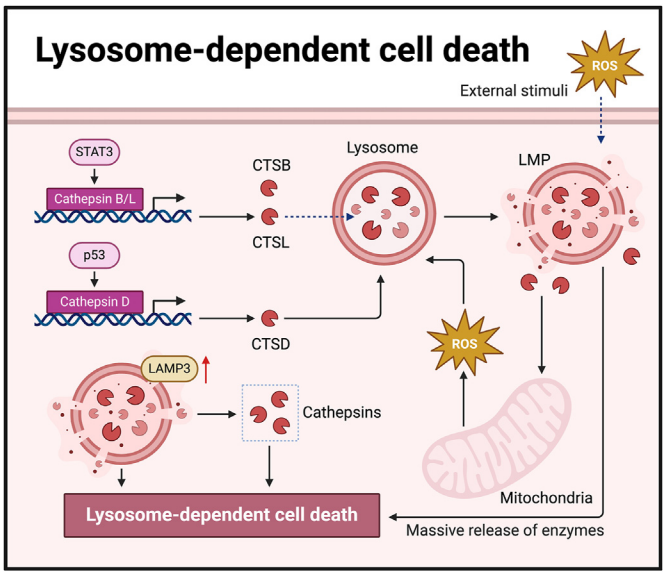

Figure 7 The key signaling pathways of lysosome-dependent cell death. STAT3 and p53 specifically upregulate the expression of cathepsins, such as *CTSB*, *CTSL*, and *CTSD*, leading to LMP to trigger cell death.

models[420]. Similarly, polyphyllin D was hit based on virtual screening as a novel lysosome-targeting compound, which has been reported to release lysosomal cathepsin to trigger lysosome-dependent cell death in HCC cells and inhibit tumor progression *in vitro* and *in vivo*[421]. Moreover, SU11652 and sunitinib were hit based on virtual screening as novel compounds that could inhibit apoptosis-resistant MCF7-BCL-2 cells. And, both SU11652 and sunitinib induced LMP to release lysosomal cathepsin, triggering lysosome-dependent cell death and inhibiting proliferation in MCF7-BCL-2 cells[422]. Furthermore, amiloride is a classical potassium-sparing diuretic agent that has antitumor potential. 5-(*N*,*N*-hexamethylene) amiloride is an amiloride derivative that has been reported to produce ROS and upregulate lysosomal cathepsin to trigger lysosome-dependent cell death in MCF-7 and MDA-MB-231 cells[423]. FV-429 is a wogonin derivative that induced LMP and upregulated CTSB to trigger lysosome-dependent cell death in Jurkat cells[424]. Additionally, macrolide antibiotic azithromycin has been reported to improve the efficacy of lansoprazole, inducing LMP to trigger lysosome-dependent cell death and inhibit proliferation in A549 cells (Supporting Information Table S6)[425]. At present, there are not many studies on the compounds targeting lysosome-dependent cell death. It is believed that with the continuous exploration of the lysosome-dependent cell death mechanism, more small-molecule compounds targeting lysosome-dependent cell death could be discovered to improve cancer therapy.

2.7. *Targeting ICD with small-molecule compounds in cancer*

2.7.1. *The key signaling pathways of ICD*

ICD is a form of RCD in which dying cells release DAMPs and tumor-associated antigens, thereby activating an adaptive immune response (Fig. 8)[426]. The term ICD was first proposed in 2005, and factors that induce ICD include viral infection, specific chemotherapy drugs such as mitoxantrone and paclitaxel, as well as physical therapies[19]. These conditions have the potential to cause the organism to create a number of DAMPs, which are then detected by pattern recognition receptors expressed by both innate and adaptive immune system components and result in an immunological response[427]. DAMPs are a class of signaling molecules released by apoptotic or stressed cells during ICD that possess immunostimulatory effects or act as "danger signals", including ATP, CRT, HMGB1, HSPs, ANXA1, and type I interferon (IFN-I)[4,428].

2.7.2. *Small-molecule compounds targeting ICD*

Notably, several compounds induce the DAMPs release (*e.g.*, CRT, ATP, and HMGB1) to trigger ICD, exerting antiproliferative activity in multiple tumors. For instance, oxaliplatin is a common chemotherapeutic drug used in CRC treatment, which has been found to induce TLR4-dependent release of CRT and HMGB1, triggering ICD to improve CRC therapy[429]. Trifluridine/tipiracil is a novel antimetabolite agent available for CRC, which has been found to increase phosphorylation of elF2α, leading to the release of CRT, ATP, and HMGB1 to trigger ICD, improving oxaliplatin-related CRC therapy[430]. Paclitaxel is a classical chemotherapeutic drug that has been found to act on TLR4 to activate IKK2 and SNAP23, and also activate the PERK and increase phosphorylation of elF2α to induce ER stress; both pathways induce the release of CRT, ATP, and HMGB1 to trigger ICD in ID8, TKO, and ID8F3 cells[431]. Rafoxanide, a classic repurposing FDA-approved anthelmintic drug available for cancer treatment, has been found to phosphorylate eIF2α to induce ER stress, leading to the release of CRT, ATP, and HMGB1 to trigger ICD in HCT116 and DLD-1 cells[432]. Similarly, lurbinectedin is an FDA-approved DNA-binding inhibitor available for small-cell lung cancer (SCLC), has been found to increase phosphorylation of elF2α, leading to the release of CRT, ATP, and HMGB1 to trigger ICD in various solid tumors[433]. Moreover, thioridazine is an FDA-approved antipsychotic drug that has been reported to activate the elF2α/ATF4/CHOP axis to induce ER stress, leading to the

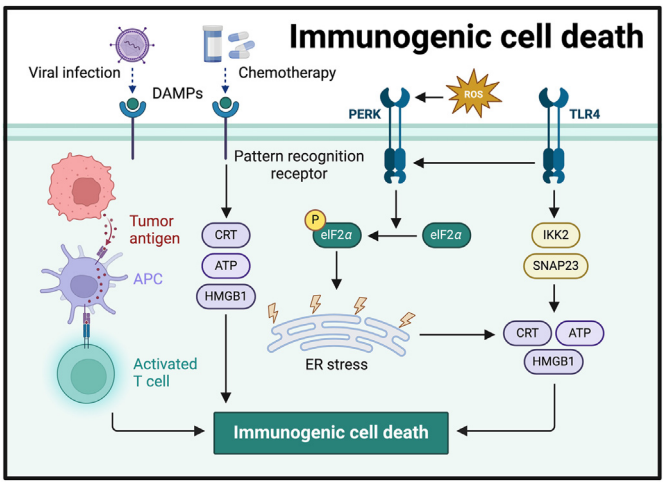

Figure 8 The key signaling pathways of ICD. ICD is commonly initiated by DAMPs to release the CRT, ATP, and HMGB1 to trigger cell death. Moreover, ROS activates the PERK to increase phosphorylation of eIF2α to induce ER stress, exposing CRT, ATP, and HMGB1 to trigger ICD.

release of CRT, ATP, and HMGB1 to trigger ICD in HT-29 and LoVo cells[434]. (*R*)-Crizotinib is a TKI that has been found to phosphorylate eIF2α to induce ER stress, leading to the release of CRT, ATP, and HMGB1 to trigger ICD in multiple tumor cells to improve chemotherapy[435]. GSK2857916 is an FDA-approved agent available for MM, which has been found to activate the PERK and increase phosphorylation of eIF2α to induce ER stress, exposing CRT, HSP70, HSP90, and IL8 with increased ATP and HMGB1 to trigger ICD in NCI-H929 cells, improving MM therapy *in vitro* and *in vivo*[436]. Similarly, belantamab mafodotin, a recent FDA-approved agent available for MM, has been found to increase CRT and HMGB1 to trigger ICD, improving MM therapy[437]. Imiquimod, an FDA-approved agent available for skin malignancies and viral warts, has been reported to produce ROS and activate the PERK/eIF2α axis to induce ER stress, leading to the release of CRT, ATP, and HMGB1 to trigger ICD in B16F10 cells, and slowing tumor growth in the B16F10 syngeneic model[438]. Dinaciclib is a CDK inhibitor that has been found to expose CRT with increased ATP and HMGB1 to trigger ICD, improving immunotherapy in solid tumors[439]. JQ1 is a BRD4 inhibitor that has been found to activate the PERK and increase phosphorylation of eIF2α to induce ER stress, leading to the release of CRT, ATP, and HMGB1 to trigger ICD in Cal27 OSCC and SCC7 murine tongue squamous cell carcinoma (TSCC) cells[440]. Sulindac sulfide is a classical non-steroidal anti-inflammatory drug that has been reported to activate the PERK and increase phosphorylation of eIF2α, upregulating ATF4 and CHOP to induce ER stress, leading to the release of CRT, ATP, and HMGB1 to trigger ICD in HCT116 cells[441]. Norcantharidin is a known demethylated analog of cantharidin with anticancer potential, which has been found to upregulate Beclin-1 and promote LC3-I conver to LC3-II to induce autophagy, leading to CRT release to induce ICD in EJ and UMUC3 cells[442]. In addition, according to the critical pharmacophore of PLD1 inhibitor VU0155069, compound A3373 has been designed and synthesized to act as a potent and selective inhibitor of PLD1, which has been found to induce the release of CRT, ATP, and HMGB1 to trigger ICD in CRC cells, inhibiting tumor proliferation *in vitro* and *in vivo*[443]. SIX2G, a novel chemically modified microtubule-targeting agent, has been reported to activate the PERK and increase phosphorylation of eIF2α, leading to the release of CRT, ATP, and HMGB1 to trigger ICD in AMO-1 cells[444]. Rose Bengal, a synthetic fluorescein dye, has been found to expose CRT and HSP90 with increased ATP and HMGB1 to trigger ICD, exerting antiproliferative activity in CT26 and HT-29 cells, and slowing tumor growth in the CT26 syngeneic model[445]. GW4064, an FXR agonist, has been found to activate the PERK and increase phosphorylation of eIF2α, leading to the release of CRT, ATP, and HMGB1 to trigger ICD in HCT116 and CT26 cells, which improved anti-PD-L1 immunotherapy in CT26 syngeneic model[446]. C-02, a degrader of critical rate-limiting enzyme hexokinase 2 in glycolysis, has been reported to induce the release of CRT, ATP, and HMGB1 to trigger ICD, improving immunotherapy in 4T1 cells and mouse models[366].

Furthermore, oleandrin, a natural product extracted from *Nerium oleander*, has been reported to activate the PERK/eIF2α/ATF4/CHOP axis to induce ER stress, leading to the release of CRT, ATP and HMGB1 to trigger ICD, exerting antiproliferative activity with IC_{50} values of 14.5 and 24.62 nmol/L in MCF-7 and MDA-MB-231 cells, reshaping the tumor microenvironment and slowing tumor growth in the EMT6 syngeneic model[447]. Similarly, MHO7 is a metabolite of the marine fungi *Aspergillus ustus*, which has been reported to activate the PERK/eIF2α/ATF4/CHOP axis to induce ER stress, leading to the release of CRT, ATP, and HMGB1 to trigger ICD, exerting antiproliferative activity with IC_{50} values of 0.96−1.75 μmol/L in TNBC cells, and slow tumor growth in the 4T1 syngeneic model[448]. Moreover, bullatacin, a natural product extracted from Annonaceae plants, has been found to expose CRT and HSP90 with increased HSP70, ATP, and HMGB1 to trigger ICD, exerting antiproliferative activity with IC_{50} values of 10 and 7 nmol/L in SW480 and HT-29 cells[449]. Dihydroartemisinin has been reported to activate CHOP to induce ER stress, triggering ICD with the increase of CRT, ATP, HMGB1, and HSP90 to reduce the viability of lewis NSCLC cells and A549 cells[450]. In addition, raddeanin A, a natural product extracted from *Anemone raddeana* Regel, has been reported to bind to TDP-43 to activate the cyclic GMP−AMP synthase/STING axis, inducing ICD with the increase of CRT, ATP and HMGB1 in B16 and MC38 cells (Supporting Information Table S7)[451]. Notably, ICD, as a stress response of tumor cells, can trigger the human body's innate and acquired immunity,

paving the way for novel tumor immunotherapy strategies. Common biomarkers for ICD include PERK, eIF2α, CRT, ATP, and HMGB1. Importantly, ICD inducers can frequently augment the anti-tumor effects of chemotherapeutic medicines, increasing the efficacy of cancer treatment.

3. The crosstalk between non-apoptotic RCD subroutines and their targeted small-molecule compounds in cancer

3.1. The crosstalk between non-apoptotic RCD subroutines

While the distinct molecular pathways and pivotal genes that underlie distinct RCD forms have been progressively clarified, an increasing body of evidence indicates that specific key regulators might concurrently assume major roles in multiple RCD subprograms, thus completing the picture of possible interaction or functional overlap between distinct subprograms. Therefore, a deeper comprehension of the molecular cascades linking RCD signaling pathways could trigger new breakthroughs and ultimately lead to the discovery of novel clinically feasible modulators for cancer therapy. Thus, this section focuses on summarizing the crosstalk among diverse forms of RCD.

AMPK is significant in modulating necroptosis, ferroptosis, and autophagy-dependent cell death. It phosphorylates and inhibits RIPK1 to regulate necroptosis while also controlling pyrimidinosome to modulate ferroptosis[140,452]. Additionally, AMPK has intricate roles in autophagy by protecting ULK1-related mechanisms from caspase-induced degradation for cellular initiation of autophagy and suppressing ULK1 to inhibit autophagy[453]. Moreover, SLC7A11 functions in both disulfidptosis and ferroptosis. The inability of cancer cells with increased SLC7A11 to convert cysteine to cystine prevents actin molecules from forming numerous disulfide bonds, which in turn causes disulfidptosis[26]. As for ferroptosis, SLC7A11 serves as the primary subunit that operates in the xc^- system by transporting cysteine into cells for glutathione synthesis; thus, suppressing *SLC7A11* expression can induce cell death *via* ferroptosis[454]. Importantly, GPX4 also functions in mediating multiple cell death processes, including autophagy, ferroptosis, necroptosis, pyroptosis, and parthanatos. Specifically, genetic evidence suggests that GPX4 exerts an inhibitory effect on necroptosis in a RIPK3-dependent manner[455]. The absence of GPX4 during pyroptosis leads to lipid peroxidation, which hinders caspase11-mediated cleavage of GSDMD and inhibits NLRP3 inflammasome-dependent caspase-1 activation. These findings highlight the broad role of GPX4 in suppressing pyroptosis[456]. As a pivotal regulatory protein in ferroptosis regulation, GPX4 effectively degrades peroxides and impedes lipid peroxidation[126]. Knockdown of GPX4 induces iron-dependent cell death while overexpression confers tolerance to stimuli triggering ferroptotic pathways[153]. Chemical-induced degradation of GPX4 (*e.g.*, alkylating agent cyclophosphamide) triggers AIFM1-dependent parthanatos and concurrently suppresses tumor growth[38]. The regulation of autophagy by GPX4 is multifaceted, encompassing the inhibition of ATG12−ATG5−ATG16L1 complex assembly by GPX4 and the facilitation of CMA-mediated degradation of GPX4 through its interaction with heat shock cognate 71 kDa protein or LAMP2A[38]. Additionally, the transcription factor p53 exerts a downregulatory effect on *SLC7A11* expression and induces ferroptosis[31]. Moreover, it selectively upregulates the expression of *CTSB/D/L* to promote lysosome-dependent cell death[414,415]. It is interesting to note that because of its dual subcellular location, p53 has two different functions in autophagy; nuclear p53 promotes *AMPK* and *Sestrin1/2* transcription to induce autophagy while cytoplasmic p53 inhibits autophagy[31]. Moreover, p53 also functions in ferroptosis and lysosome-dependent cell death. It is noteworthy that members of the deubiquitinase family, such as USP8/11/18/48 and OTUD1/4, along with the heat shock protein family (HSP70/90/A8), exert precise regulatory effects on multiple RCD subroutines[313,314,457−460].

Significantly, based on the continuous elucidation of the mechanisms underlying various subprograms of RCD in tumors, these subprograms are considered predictive of clinical prognosis and drug sensitivity in specific tumor types, such as TNBC[461]. Moreover, a number of RCD visualization platforms have been developed, such as XDeathDB, which enables thorough interaction analysis between various tumor cell death modes and supports the search for new medications that target system-driven induction of cell death[462]. Lastly, further investigation is warranted into important biological events occurring at the core of distinct RCD subprograms, such as phase separation and alternative splicing[133,310].

3.2. Small-molecule compounds targeting two or more non-apoptotic RCD subroutines

Importantly, there are multiple compounds that induce two or more RCD subroutines simultaneously by modulating critical overlap proteins (Fig. 9A). For instance, neoalbaconol is a PDK1 inhibitor that has been reported to inhibit PI3K/Akt to suppress energy metabolic enzyme hexokinase 2, leading to energy crisis to induce autophagy-dependent cell death and necroptosis in C666-1 and HK1 cells, reducing tumor viability and progression *in vitro* and *in vivo*[95]. Moreover, auriculasin has been reported to produce ROS, accumulating Fe^{2+} to induce ferroptosis and activating KEAP1 to dephosphorylate AIFM1 to induce oxeiptosis, inhibiting proliferation and invasion in CRC cells[223]. Similarly, β-lapachone has been reported to produce ROS, activating RIPK1 to induce necroptosis and activating PARP-1 to induce AIF nuclear translocation to trigger parthanotos, inhibiting proliferation in HCC cells[291]. Furthermore, there are various compounds that induce two or more RCD subroutines by separately modulating core proteins under the specific RCD pathways (Fig. 9B). For instance, according to the critical pharmacophore of classical antitumor drugs sorafenib and gefitinib, a series of quinazolinyl−arylurea derivatives were designed and synthesized to test the activities; among them, compound **7j** showed the optimal antiproliferative activity, which induced autophagy-dependent cell death by inhibiting PI3K/Akt/mTOR, upregulating the phosphorylation of ULK1 while downregulating p62; and, **7j** also induced ferroptosis by inhibiting GPX4[88]. Moreover, nobiletin has been found to separately induce autophagy-dependent cell death *via* upregulating LC3-II, and induce GSDMD/GSDME-dependent pyroptosis *via* upregulating ROS and IL-1β, exerting antiproliferative activity in OV cells[123]. Similarly, osthole has been found to separately induce autophagy-dependent cell death *via* upregulating LC3 and LC3-II, and induce GSDME-mediated pyroptosis, reducing the viability of OV cells[124]. Liproxstatin-1 is a classical ferroptosis inhibitor that has been found to separately induce autophagy-dependent cell death *via* upregulating LC3, and induce GSDME-dependent pyroptosis *via* activating caspase-3, exerting compelling antiproliferative activity in leukemia cells[122]. Sophflarine A has been found to separately induce autophagy-dependent cell death by producing ROS to inhibit PI3K−Akt−mTOR and p62, upregulating LC3-II, and induce GSDMD-dependent pyroptosis *via* activating the NLRP3 inflammasome and caspase-1 in NSCLC cells, inhibiting tumor proliferation *in vitro* and *in vivo*[94]. Moreover, gallic acid has been reported to

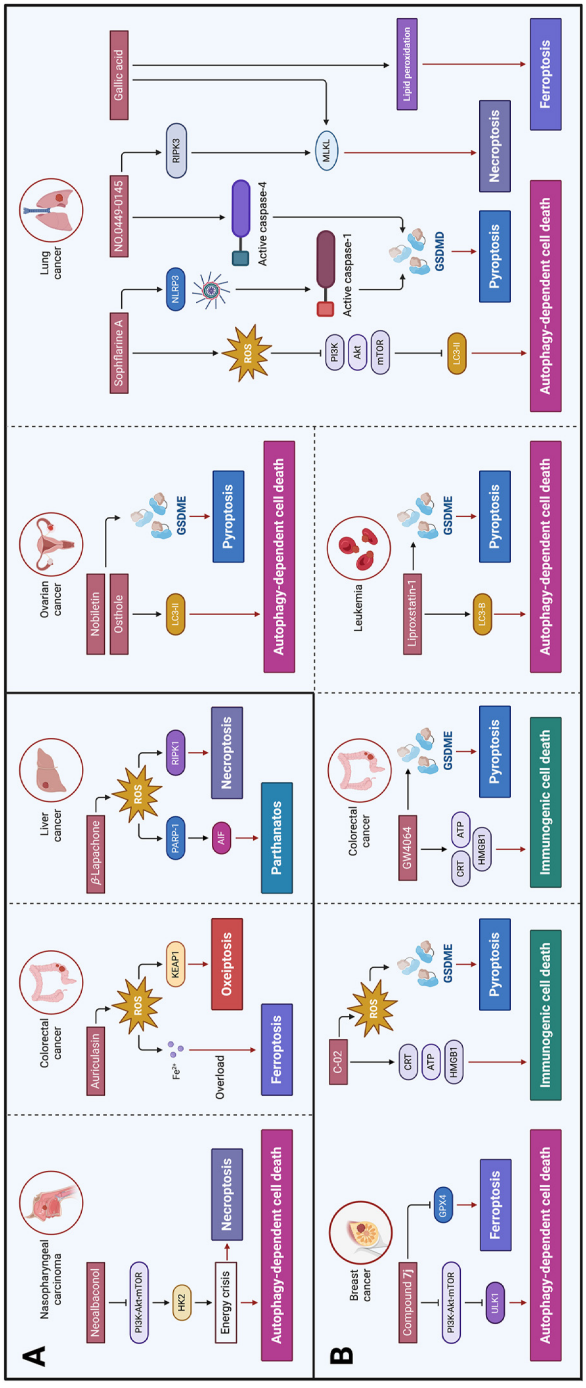

Figure 9 The crosstalk between non-apoptotic RCD subroutines and their targeted small-molecule compounds in cancer. (A) Small-molecule compounds that induce two or more RCD subroutines by modulating the same protein. (B) Small-molecule compounds that induce two or more RCD subroutines by separately modulating their core proteins.

separately induce lipid peroxidation-mediated ferroptosis and MLKL-mediated necroptosis in HeLa, H446, and SH-SY5Y cells[233]. No.0449-0145, a novel APE1 inhibitor, has been found to separately upregulate the phosphorylation of RIPK3 and MLKL to induce necroptosis and activate caspase-4 and GSDMD with the increased IL-1β to induce pyroptosis, inhibiting proliferation in A549 and NCI-H460 cells and slowing tumor growth in the NCI-H460 xenograft model[279]. C-02, a degrader of critical rate-limiting enzyme hexokinase 2 in glycolysis, has been reported to separately induce GSDME-dependent pyroptosis *via* producing ROS to release cytochrome c and activating caspase-3, induce ICD with the increased CRT, ATP, and HMGB1, inhibiting proliferation and improving immunotherapy in 4T1 cells and mouse models[366]. Similarly, GW4064, an FXR agonist, has been found to separately induce GSDME-dependent pyroptosis *via* upregulating BAX to activate caspase-3 and induce ICD with the increased CRT, ATP, and HMGB1 *via* activating the PERK and increasing phosphorylation of eIF2α, inhibiting proliferation and improving immunotherapy in CRC cells and mouse models[363,446].

Additionally, there are also multiple compounds have been found to induce different RCD subroutines in different types of tumors to exert antitumor activities. For instance, flubendazole, a classic repurposing FDA-approved anthelmintic drug available for cancer therapy, has been found to activate EVA1A, Beclin-1 and LC3-II while downregulating p62 to induce autophagy-dependent cell death and inhibit the proliferation and migration of MDA-MB-231 and MDA-MB-468 cells; in castration-resistant PRAD, flubendazole has been found to activate p53 to suppress *SLC7A11* gene transcription, then downregulating GPX4 to induce ferroptosis to inhibit tumor proliferation *in vitro* and *in vivo*; and, in GBM, flubendazole has been reported to activate NF-κB and NLRP3, inducing caspase-1 to cleave GSDMD, triggering pyroptosis to inhibit tumor proliferation *in vitro* and *in vivo*[109,229,330]. Similarly, shikonin has been reported to inhibit PI3K/Akt/mTOR to induce autophagy-dependent cell death and inhibit the proliferation of SNU-449 and Hep3B cells; in OV, shikonin has been reported to overcome chemoresistance caused by cisplatin prolonged treatment, restoring drug sensitivity and upregulating HMOX1 with the accumulation of Fe^{2+} to induce ferroptosis *in vitro* and *in vivo*; in BLCA, shikonin has been reported to produce ROS to activate RIPK1 and RIPK3, inducing necroptosis to inhibit tumor proliferation[93,214,261]. Honokiol has been reported to inhibit PI3K/Akt/mTOR while activating ER stress, producing ROS and upregulating the phosphorylation of ERK, inducing autophagy-dependent cell death in NBs and OS, and exerting promising antitumor efficacy *in vitro* and *in vivo*; and, honokiol has also been found to upregulate HMOX1, leading to lipid peroxidation to induce ferroptosis in AML cells[101,102,213]. PPVI has been reported to produce ROS in NSCLC cells. On one hand, ROS inhibited mTOR signaling to induce autophagy-dependent cell death. On the other hand, ROS activated NF-κB, NLRP3 inflammasome, and caspase-1, cleaving GSDMD to induce pyroptosis[82,339]. In addition, PPVI also has been found to suppress STAT3 to inhibit *GPX4* transcription, inducing ferroptosis to inhibit the proliferation and invasion in HCCLM3 and Huh-7 cells[217]. Moreover, dihydroartemisinin has also been reported to inhibit Wnt/β-catenin to induce autophagy to reduce the viability of MM cells; dihydroartemisinin has also been found to induce ferritin autophagy to unstable iron, inhibiting GPX4 to induce ferroptosis, showing promising cancer therapeutic potential *in vitro* and *in vivo*; in ESCC, dihydroartemisinin has been found to activate caspase-3 and -8 to cleave GSDME, inducing pyroptosis to inhibit tumor progression *in vitro* and *in vivo*; and, in BC, dihydroartemisinin has been found to upregulate AIM2 to activate caspase-3 to cleave GSDME, inducing pyroptosis in MCF-7 and MDA-MB-231 cells to

exert antitumor activity *in vitro* and *in vivo*; in addition, dihydroartemisinin has been reported to activate CHOP to induce ER stress, triggering ICD with the increase of CRT, ATP, HMGB1, and HSP90 to reduce the viability of lewis NSCLC cells and A549 cells[65,201,369,370,450]. Berberine has been reported to inhibit Akt/mTORC1 to induce autophagy-dependent cell death in ALL cells; in OV, berberine also increased the phosphorylation of RIPK3 and MLKL, which enhanced cisplatin-induced necroptosis to inhibit tumor proliferation[91,256]. Moreover, metformin is a classic diabetes drug that has been found to AMPK to inhibit mTOR, activating ULK1 to induce autophagy-dependent cell death and reduce the viability of MM cells; and, metformin has been reported to upregulate BAX *via* AMPK/SIRT1/NF-κB pathway, activating caspase-3 to cleave GSDME and inducing pyroptosis in multiple tumors; in addition, in ESCC, metformin has also been found to upregulate miR-497 while suppressing PELP1, inducing GSDMD-mediated pyroptosis to inhibit proliferation *in vitro* and *in vivo*[59,356,357]. DHA, an essential polyunsaturated fatty acid that induces autophagy-dependent cell death *via* upregulating OSGIN1 to produce ROS, activating AMPK and inhibiting mTOR in MCF-7 cells, has been found to activate NF-κB, caspase-1 and GSDMD with increased IL-1β and HMGB1, inducing pyroptosis to inhibit proliferation in MDA-MB-231 cells[67,337]. Moreover, thioridazine is an FDA-approved antipsychotic drug that has been reported to activate AMPK and inhibit Wnt/β-catenin, upregulating LC3-II to induce autophagy in GBM cells; in CRC, thioridazine has also been found to activate the elF2α/ATF4/CHOP axis to induce ER stress, leading to the release of CRT, ATP and HMGB1 to trigger ICD[64,434]. Importantly, sorafenib, the first FDA-approved multi-target anticancer drug available for HCC and advanced RCC, has been reported to inhibit system xc^- to induce ferroptosis in HCC; and, sorafenib has also been found to induce RIPK1-mediated necroptosis in MM cells; in addition, sorafenib has also been found to activate caspase-1 to induce pyroptosis in macrophages, enhancing anti-tumor immunity *via* natural killer cells in HCC[164,287,328]. Simvastatin is a classic cholesterol-lowering drug that has been reported to induce ferroptosis in TNBC; in NSCLC, simvastatin has been found to activate NLRP3 to induce caspase-1-mediated pyroptosis; in GC, simvastatin has been found to activate caspase-3 to induce GSDME-mediated pyroptosis, exerting promising anti-tumor efficacy *in vitro* and *in vivo*[197,333,334]. Moreover, classical proteasomal inhibitors MG132 and bortezomib have been found to activate RIPK3 and MLKL to induce necroptosis in leukemia cells; in MM, MG132 and bortezomib have also been found to block the interaction between BCL-2 and BAX, upregulating BAX to activate caspase-3, -6, -7 and -9 to cleave GSDME to induce pyroptosis[280,348]. BI 2536 is also a PLK1 inhibitor, which induced necroptosis in castration-resistant PRAD; and, BI 2536 has also been found to activate caspase-3 to cleave GSDME, inducing pyroptosis to exert antitumor activity in CRC, OV and ESCC[296,359–361]. 5-FU, a classical chemotherapeutic drug in CRC therapy, has been reported to increase TNF-α autocrine and activate RIPK1 to induce necroptosis; and, 5-FU has also been found to activate caspase-3 to cleave GSDME, inducing pyroptosis and inhibiting proliferation in GC cells[257,355]. Triptolide has been reported to upregulate RIPK1, RIPK3, and MLKL phosphorylation to induce necroptosis in HCC cells; in HNC, triptolide has been reported to inhibit HK-II to activate BAX and BAD, then activate caspase-3 to cleave GSDME, inducing pyroptosis to inhibit tumor proliferation[263,372]. In addition, JQ1 is a BRD4 inhibitor that has been found to activate the NLRP3 inflammasome and caspase-1 with the increased IL-1β, inducing GSDMD-dependent pyroptosis to inhibit the proliferation of RCC cells; and, in OSCC and TSCC, JQ1 has also been found to activate the PERK and increase phosphorylation of elF2α to induce ER stress, leading to the release of CRT, ATP and HMGB1 to trigger ICD in OSCC and TSCC cells[332,440].

Therefore, to better develop cancer treatment drugs from the perspective of regulating RCD, we need to identify the vulnerability of different cancers and use appropriate RCD to injure their vital doors. For example, in tumors that are highly GPX4-dependent, inhibiting GPX4 to trigger ferroptosis is a very sensible strategy. Similarly, some tumors promote high mutation and malignant proliferation of tumors by weakening overall autophagy levels, in which case activation of autophagy is necessary. Conversely, in some highly inflammatory tumors, the tumor adapts to the stimulation of inflammatory factors. Under such conditions, the tumor will be less responsive to the activated necroptosis. Therefore, it is wise to find the susceptibility to cancer by multi-omics means. Alternatively, RCD is not present alone and the progression of one RCD affects one or more RCDs, so an appropriate regulatory RCD network is also recommended.

4. Potential clinical applications of small-molecule compounds targeting RCD subroutines

Encouragingly, there is already a growing number of compounds specifically targeting RCD subroutines that have demonstrated remarkable preclinical antitumor efficacy. In line with this progress, we conducted a search on clinicaltrials.gov and found several compounds currently undergoing or having completed clinical trials for cancer-related applications. For instance, the clinical phase 1/2 study of the safety and efficacy of the classical FIN APR-246 combined with pembrolizumab in BLCA, GC, NSCLC, urothelial carcinoma, and advanced solid tumors has been completed (NCT04383938) with few adverse reactions (*e.g.*, dizziness, nausea and vomiting). And, the clinical phase 1/2 study of APR-246 combined with venetoclax or azacitidine in TP53-mutated AML has also been completed (NCT04214860, NCT03072043) with overall response rates >60%. Taken together, APR-246 is well tolerated with acceptable safety and deserves further clinical study. Moreover, the clinical phase 1 study of autophagy inducer ABTL0812 in advanced solid tumors has been completed (NCT02201823) with satisfactory safety and tolerability. Similarly, another autophagy inducer, also the classical mTOR inhibitor AZD2014 combined with anastrozole is in a phase 1/2 clinical trial for the treatment of hormone receptor-positive recurrent or metastatic endometrial cancer (NCT02730923). BI 2536 is a PLK1 inhibitor, which can induce tumor necroptosis and pyroptosis; the efficacy, safety, and pharmacokinetics of BI 2536 in SCLC have been evaluated in a phase 2 trial (NCT00412880) under a dose of 200 mg every 21 days. Chidamide is a histone deacetylase inhibitor that can induce tumor ferroptosis and pyroptosis; the clinical phase 3 study of chidamide combined with exemestane in hormone-receptor positive advanced BC has been completed (NCT02482753) with satisfactory safety and efficacy. Moreover, the clinical phase 1 study of ICD inducer dinaciclib combined with pembrolizumab in chronic lymphocytic leukemia (CLL), MM, or DLBCL has been completed (NCT02684617) with satisfactory safety and tolerability and acceptable adverse reactions (*e.g.*, fatigue, nausea, anemia, constipation, diarrhea, decreased platelet count and cough). In addition, the clinical phase 2 study of necroptosis inducer birinapant has been carried out in epithelial OV, peritoneal neoplasms, and fallopian tube neoplasms (NCT01681368).

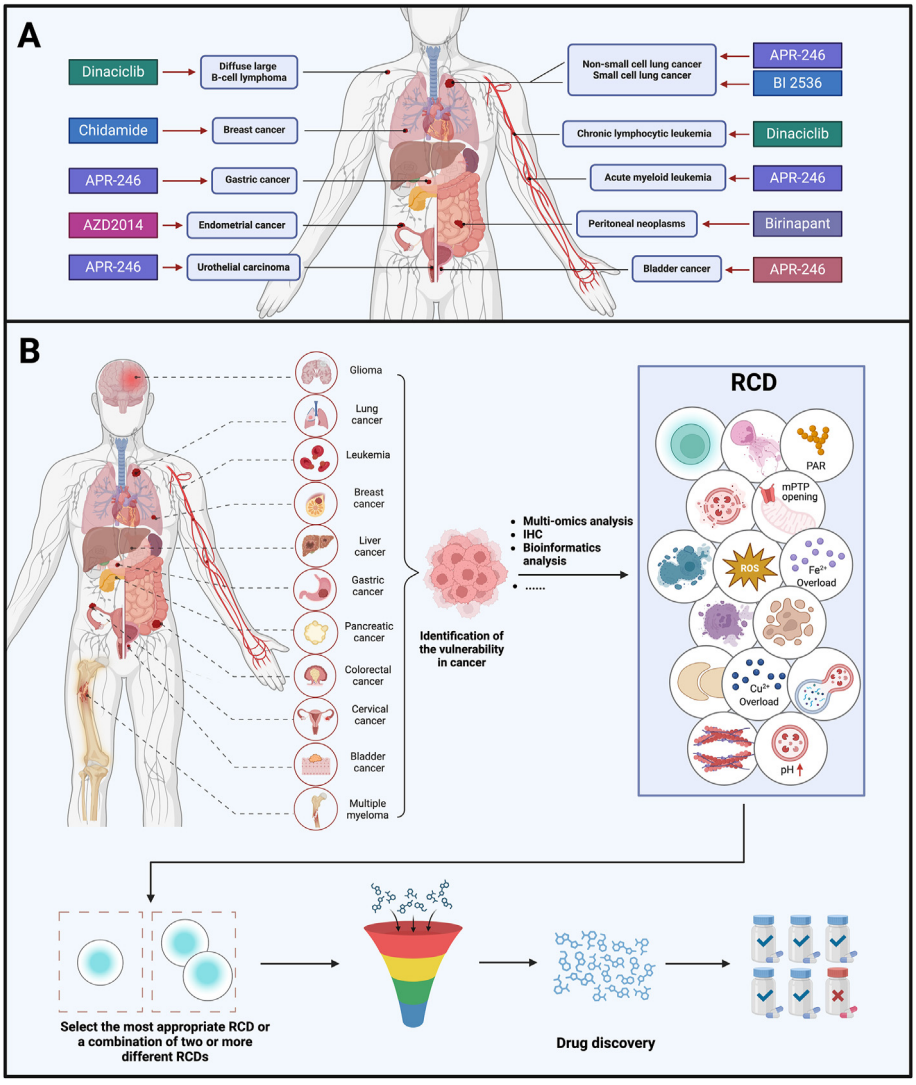

Figure 10 Small-molecule compounds targeting RCD subroutines in cancer clinical trials and future perspectives of targeting RCD.

Overall, the majority of small molecules that target RCD subroutines have compelling safety and tolerability, with only a few common and manageable adverse reactions, such as fatigue, dizziness, nausea, and vomiting. As a result, we anticipate that an increasing number of small-molecule drugs targeting RCD subroutines will undergo clinical trials with the aim of successfully improving cancer therapy (Fig. 10 and Supporting Information Table S8).

5. Concluding remarks and future perspectives

Of note, RCD is a significant homeostatic mechanism for cell maintenance of tissue morphology and function and is essential for development, immunity, and tissue balance[463]. Unlike the cellular uncontrollability of accidental cell death, the occurrence of RCD is controlled by a highly organized cascade of signals[4]. More importantly, tumor cells frequently survive by evading RCD, resulting in tumor worsening or recurrence[244]. Therefore, it is anticipated that a deeper comprehension of the physiological function of multiple RCD mechanisms and their associated signaling pathways would allow for more precise manipulation of RCD to improve cancer therapy[1].

Due to tumors often developing acquired resistance to apoptosis, there is an urgent need to explore novel alternative therapies that can induce tumor cell death through non-apoptotic mechanisms, which will also help enhance the sensitivity of apoptotic drugs[1,346]. In this review, we focus on summarizing the regulatory mechanisms of emerging non-apoptotic RCD subroutines, including autophagy-dependent cell death, ferroptosis, cuproptosis, disulfidptosis, necroptosis, pyroptosis, alkaliptosis, oxeiptosis, parthanatos, MPT-driven necrosis, entotic cell death, NETotic cell death, lysosome-dependent cell death, and ICD, which hope to explore more apoptotic alternative therapies for cancer[1]. Among them, autophagy-dependent cell death, ferroptosis, necroptosis, and pyroptosis are emerging as research hotspots because of their efficacy similar to apoptosis in producing tumor regression and preventing relapse[31]. Moreover, ICD, as a stress response of tumor cells, can activate the innate and post-acquired immunity of the human body, providing new directions for tumor immunotherapy[464]. Currently, a number of ICD inducers, including the common medication oxaliplatin, are utilized in clinical cancer treatment. The impact of these medicines is frequently more noticeable in cancer therapy than that of other medications[429,464]. Importantly, ICD inducers can often enhance the anti-tumor effects

of chemotherapy drugs[430,434]. In addition, similar to ferroptosis is triggered by iron overload, cuproptosis is caused by copper overload and, like ferroptosis, is directly tied to mitochondrial metabolism[25]. Therefore, it is anticipated that cuproptosis will be found to be a fantastic alternative therapy for apoptosis with a thorough investigation of its mechanism. Disulfidptosis, a unique RCD subroutine associated with the actin cytoskeleton that was recently revealed, quickly attracted significant interest in the study of cell death and may have provided new avenues for cancer therapy[26]. Furthermore, crosstalk between non-apoptotic RCD subroutines was also summarized in order to understand the link between the various RCD pathways and facilitate pharmacological intervention.

Many efforts have been made to manipulate these RCD subroutines for the purpose of cancer treatment. In this review, we systematically summarize compounds that induce autophagy-dependent cell death, 64 compounds that induce ferroptosis, 40 compounds that induce necroptosis, 51 compounds that induce pyroptosis, 1 compound that induces alkaliptosis, 1 compound that induces oxeiptosis, 8 compounds that induce parthanatos, 1 compound that induces MPT-driven necrosis, 3 compound that induces entotic cell death, 1 compound that induces NETotic cell death, 8 compounds that induce lysosome-dependent cell death and 22 compounds that induce ICD, all of which have been developed for cancer therapy. Among them, many compounds induce two or more RCD subroutines by modulating the same protein; several compounds induce two or more RCD subroutines by separately modulating their core proteins[95,124]. In addition, some compounds were found to induce different RCD subroutines to exert antitumor activity in different types of tumors[109,229,330]. These diverse compound scaffolds and detailed pharmacological regulatory mechanisms are expected to contribute to the development of more RCD inducers in cancer therapy. Notably, there are already small-molecule compounds targeting non-apoptotic RCD subroutines that have entered cancer clinical studies, such as the classic FIN APR-246, the autophagic inducer ABTL0812 and the ICD inducer Dinaciclib; most of which have shown good efficacy and compelling safety and tolerability in clinical trials. Furthermore, several emerging technologies are also working to develop small-molecular drugs targeting RCD. For instance, artificial intelligence technology can incorporate enormous chemical and biological data to build high-quality machine learning models and assist in target screening, molecular structure-chemical spatial analysis, ligand-receptor interaction simulation, and three-dimensional quantitative structure-activity relationship analysis to guide the discovery and optimization of lead compounds. The DNA-encoded chemical library approach can enable high-throughput, quick, and efficient detection of small molecular-protein interactions through affinity-based screening of targets[465]. Gene editing technology can edit target genes at the genome level, highly simulate cancer mechanism and progression, and substantially simplify and reduce the modeling cycle[466]. Moreover, targeted protein degradation technology has become a new hot technology in drug development due to its low protein restriction, high specificity, and fast action time[467]. In addition, cryo-electron microscopy offers the necessary information on structure−activity relationships, which reduces the number of compounds that must be synthesized and verified, allowing for more efficient screening of therapeutic candidates with fewer iterations[468]. These new technologies have the potential to considerably accelerate RCD drug discovery and are anticipated to yield further approaches for precise RCD manipulation.

In summary, we provide a comprehensive perspective of the regulatory mechanisms of non-apoptotic RCD subroutines as well as existing interventions aimed at identifying alternative therapies to address apoptotic resistance in cancer to cause tumor regression and prevent recurrence. In addition, we also hope to provide clues for the discovery of more novel RCD subroutines and drugs, and ultimately to rationally manipulate one or more RCD subroutines to improve potential clinical cancer therapy in the near future.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Youdao AI translation to polish some sentences. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Author contributions

Xin Jin: Data curation, Writing − original draft. **Wenke Jin:** Data curation, Writing − original draft. **Linlin Tong:** Data curation, Visualization. **Jia Zhao:** Conceptualization, Supervision, Writing − review & editing. **Lan Zhang:** Conceptualization, Supervision, Writing − review & editing. **Na Lin:** Conceptualization, Supervision, Writing − review & editing.

Conflicts of interest

All authors declare that they have no competing interests.

Appendix A. Supporting information

Supporting information to this article can be found online at https://doi.org/10.1016/j.apsb.2024.04.020.

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