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Review Article

Emerging role of necroptosis, pyroptosis, and ferroptosis in breast cancer: New dawn for overcoming therapy resistance

Bifei Fu [a,1], YuMing Lou [a,1], Pu Wu [b], Xiaofeng Lu [a,2,*], Chaoyang Xu [a,b,2,*]

[a] Department of Breast and Thyroid Surgery, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, Zhejiang 321000, China
[b] Central Laboratory, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, Zhejiang 321000, China

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ABSTRACT

Breast cancer (BC) is one of the primary causes of death in women worldwide. The challenges associated with adverse outcomes have increased significantly, and the identification of novel therapeutic targets has become increasingly urgent. Regulated cell death (RCD) refers to a type of cell death that can be regulated by several different biomacromolecules, which is distinctive from accidental cell death (ACD). In recent years, apoptosis, a representative RCD pathway, has gained significance as a target for BC medications. However, tumor cells exhibit avoidance of apoptosis and result in treatment resistance, which emphasizes further studies devoted to alternative cell death processes, namely necroptosis, pyroptosis, and ferroptosis. Here, in this review, we focus on summarizing the crucial signaling pathways of these RCD in BC. We further discuss the molecular mechanism and potentiality in clinical application of several prospective drugs, nanoparticles, and other small compounds targeting different RCD subroutines of BC. We also discuss the benefits of modulating RCD processes on drug resistance and the advantages of combining RCD modulators with conventional treatments in BC. This review will deepen our understanding of the relationship between RCD and BC, and shed new light on future directions to attack cancer vulnerabilities with RCD modulators for therapeutic purposes.

Introduction

Breast cancer (BC) is one of the most prevalent malignancies among women, with an annually increased incidence that poses a severe threat to women's health and lives. The current state of BC treatment, which mostly consists of surgery, radiation, chemotherapy, and targeted therapy, is still inadequate [1]. There are still a considerable number of patients acquiring drug resistance after systemic treatments, which appears to be the main obstacle to therapeutic advances. With in-depth research on the mechanism of cancer drug resistance, avoidance of apoptosis is one of the most commonly recognized characteristics [2]. Therefore, for improving the prognosis of BC patients, the search for therapeutic agents that induce nonapoptotic cell death pathways is expected to be a significant method for reversing drug resistance and is anticipated to act as the foundation of translational medicine in the future.

Cell death fundamentally contributes to the maintenance of physiological homeostasis by eliminating damaged cells, and may also be an aberrant pathological response to damaging stimuli [3]. According to morphology, biochemistry, and function, cell death modes are categorized into regulated cell death (RCD) and accidental cell death (ACD). RCD is characterized by the autonomous and orderly death of cells controlled by genes in order to maintain organismal development or tissue renewal [4]. Prior to more in-depth research on tumor cell biology and a thorough evaluation of cancer therapy mechanisms, apoptosis was thought to be the main RCD subtype. Currently, the newly discovered types of RCD mainly include necroptosis, pyroptosis, and ferroptosis, which can occur with or without exogenous or intracellular perturbations [5,6]. In addition, each of these RCD patterns is induced and transmitted by complex mechanisms that show a considerable degree of interconnection [7].

Different lethal subroutines during RCD can regulate cancer progression and response to therapy. At present, increasing evidence reveals that BC cells have developed numerous ways to avoid apoptosis,

* Corresponding authors at: Department of Breast and Thyroid Surgery, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, Zhejiang 321000, China.
E-mail addresses: luxiaofeng2007@hotmail.com (X. Lu), xuchaoyang@zju.edu.cn (C. Xu).
[1] These authors contributed equally to this work.
[2] These authors jointly supervised this work.

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which has turned out to be one of the characteristics of drug resistance. Therefore, paying attention to different RCD pathways may be a significant and promising direction for BC treatment, and further research into modulators of these pathways is essential for the clinical application of RCD-related therapies in BC. In this review, we introduce the molecular mechanisms of necroptosis, pyroptosis, and ferroptosis and their biological functions in BC. More importantly, we comprehensively describe several therapeutic agents targeting these RCD pathways in order to provide new targets and ideas for drug resistance in BC.

Biological functions of necroptosis in BC

Necroptosis, a type of RCD triggered by perturbations of extracellular or intracellular homeostasis, depends on the phosphorylation of mixed-lineage kinase-like (MLKL) by receptor interacting kinase-1 (RIPK1) and receptor interacting kinase-3 (RIPK3) [8]. Cell surface-specific death receptors, including (but not limited to) FAS and TNFR1 [9,10], or pathogen recognition receptors (PRRs), including TLRs and Z-DNA binding protein 1 (ZBP1) [11,12], initiate the necroptotic process. This process requires RIPK3, which is activated by three distinct processes. First, TNFR1 ligation activates RIPK1, which then interacts with RIPK3 via two molecules' shared RIP homology interaction motifs (RHIM) [13,14]. Similarly, TLR-3 and TLR-4 activation recruits the adaptor, which contains the RHIM domain that enable them to bind and activate RIPK3 [11]. Last but not least, a RIPK3-activating RHIM is also present in the cytosolic nucleic acid sensor ZBP1 [15]. Subsequently, RIPK3 regularly phosphorylated MLKL, resulting in the formation of MLKL oligomers that translocate to the plasma membrane. Eventually, this process results in cell death, which is characterized by permeabilization of the plasma membrane and cell swelling (Fig. 1) [16,17].

In triple-negative breast cancer (TNBC), AQP1 overexpression represses RIPK1-mediated necroptosis and promotes cancer progression and metastasis [18]. Parkin overexpression is linked to a worse prognosis in BC patients, and parkin facilitates the polyubiquitination of RIPK3 [19]. In addition, Zheng et al. reported that necroptosis-related miRNAs are associated with the rate of metastasis in BC patients [20]. Additionally, a recent study showed that deletion of ZBP1 prevents tumor cells from necroptosis during the course of a tumor's development, which prevents tumor metastasis in the MVT-1 BC model [21]. Liu et al. demonstrated that inhibiting MLKL or knocking out RIPK3 significantly decreases tumorigenicity in some BC cell lines by reducing the production of NF-κB-driven proinflammatory cytokines [22]. Furthermore, a recent study revealed that RIPK1-dependent necroptosis in TNBC promotes vasculogenic mimicry formation by activating RIPK1/p-AKT/eIF4E signaling and provides a potential therapeutic target for BC [23].

Biological functions of pyroptosis in BC

Pyroptosis, a modality of RCD that primarily depends on the formation of plasma membrane pores by the gasdermin (GSDM) protein family, frequently occurs as a result of inflammatory caspase activation [8]. At a molecular level, pyroptosis is triggered by the activation of one or more caspases, including caspase-1, caspase-3, murine caspase-11, and its human homologs caspase-4 and caspase-5 [24]. Thus, the inflammatory cytokines IL-1β and IL-18 often (if not always) undergo activation and secretion during pyroptosis, which mediates robust pro-inflammatory effects [25,26]. When a host is triggered by different stimuli, these caspases cleave members of the GSDM superfamily at the location of the linker region and release the N-terminal pore-forming domain (PFD) from the C-terminal repressor domain (CT). As a result, the N-terminal PFD oligomerizes and creates pores in the cell

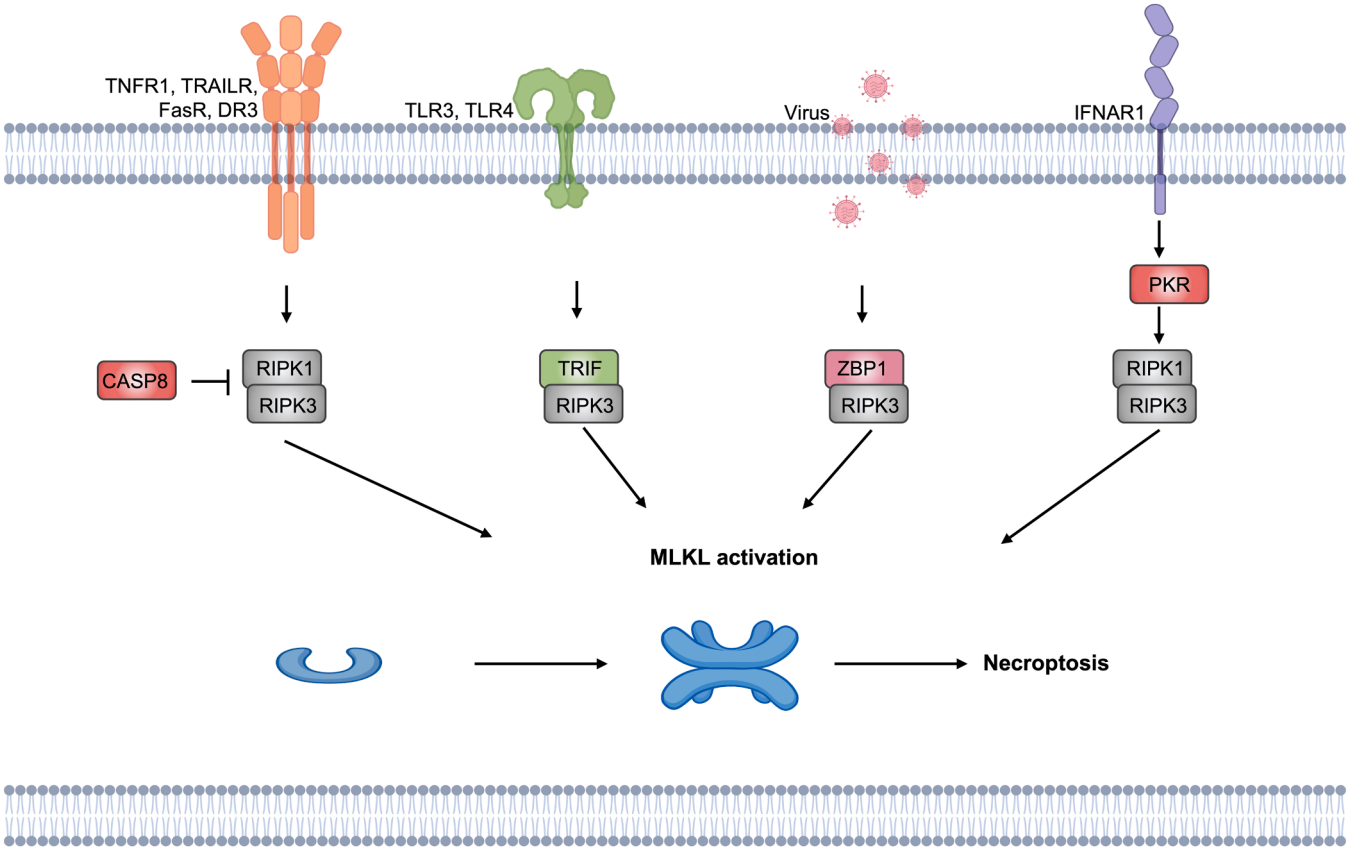

Fig. 1. Molecular mechanism of necroptosis. ZBP1 and cell surface death receptors, such as FasRs, TNFR, IFN receptors, and TLRs, initiate necroptosis, and RHIM-containing downstream proteins bind to RIPK3. The necrosome is then developed, which causes cell lysis.

membrane, causing cells to swell, chromatin to degrade, and proinflammatory substances to be released (Fig. 2) [27–29].

GSDMB could encourage the development of drug resistance in patients with different HER2-positive BC on trastuzumab treatment [30]. As early as 2008, Kim et al. examined the methylation of the GSDME and discovered that a CpG site might be used as a BC marker [31]. Using publicly available data from The Cancer Genome Atlas, Croes et al. found that GSDME gene methylation significantly affects patients' 5-year survival rates, indicating that GSDME could be used as a marker for the early detection and prognosis of patients [32]. In addition, more recent studies revealed that pyroptosis is crucial for regulating the immunoreaction against breast cancer and that the immunological environment in breast cancer is diverse and dynamic [33,34]. According to research by B. Guo et al., the inflammatory microenvironment that is created by the activation of the NLRP3 inflammasome promotes BC progression. Therefore, pyroptosis may have a dual role in BC.

Biological functions of ferroptosis in BC

Ferroptosis is a unique form of RCD initiated by oxidative perturbations of the intracellular microenvironment that can be inhibited by iron chelators and lipophilic antioxidants [8]. The morphological characteristics of ferroptosis distinguish it from other modes of death by having reduced mitochondrial volume, a ruptured mitochondrial outer membrane, a diminished or absent mitochondrial crest, and a normal-sized nucleus without nuclear concentration [35]. Under normal conditions, polyunsaturated fatty acids (PUFAs) are frequently oxidized by lipoxygenases, such as 12- and 15-lipoxygenases, but the levels of lipoxygenase-oxidized PUFAs are rapidly decreased by the lipid repair enzyme glutathione peroxidase 4 (GPX4) and its cofactor glutathione (GSH) [36]. The ferroptosis process is triggered by the suppression of the cystine-glutamate antiporter (system X_C^-, consisting of subunits SLC3A2 and SLC7A11), causing decreased GSH biosynthesis and GPX4 inactivation. Subsequently, the cell dies as a result of extreme lipid peroxidation (Fig. 3A) [37]. Besides oxidative perturbations, ferroptosis is regulated by other pathways, such as the p53 pathway in cancer. It can be inhibited by several pathways, including the NAD(P)H-ferroptosis suppressor protein 1-ubiquinone (NAD(P)H-FSP1-CoQ_{10}) pathway, the GCH1-BH4 pathway, and the DHODH-CoQH2 system (Fig. 3B–D) [38–40].

A recent study showed that iron-regulatory genes are highly overexpressed in TNBC compared to non-TNBC tumors. In particular, a significant number of low-level iron export transporters together with highly expressed iron import transferrin receptors are observed in TNBC [41]. A Canadian cohort study showed that heme iron is positively correlated with the risk of the ER negative or PR negative BC subtypes in postmenopausal women, which also found a low risk of breast cancer associated with dietary iron supplementation [42]. However, a more recent study showed that high iron levels in the inflammatory microenvironment may facilitate the progression and metastasis of breast cancer and that ferroptosis is involved in the brain metastasis of BC [43]. According to a European randomized controlled research, the incidence of ER-negative breast cancer is positively correlated with serum transferrin level [44]. Furthermore, BC is characterized by abnormal amino acid and lipid metabolism, which is tightly associated with the regulation of ferroptosis. According to research by Chen et al., the absence of cystine in TNBC cells is particularly deadly because it induces ferroptosis in TNBC cells by activating the GCN2-eIF2α-ATF4 signaling pathway [45]. ACSL4, a member of the long-chain acyl coenzyme A (acyl-CoA) synthase (ACSL) family, increases the sensitivity of BC to ferroptosis [46]. In addition, a predictive multigene signature of BC based on genes that are differently expressed in ferroptosis was developed in a recent study [47,48]. Taken together, these findings indicate that ferroptosis plays a crucial role in inhibiting tumor growth.

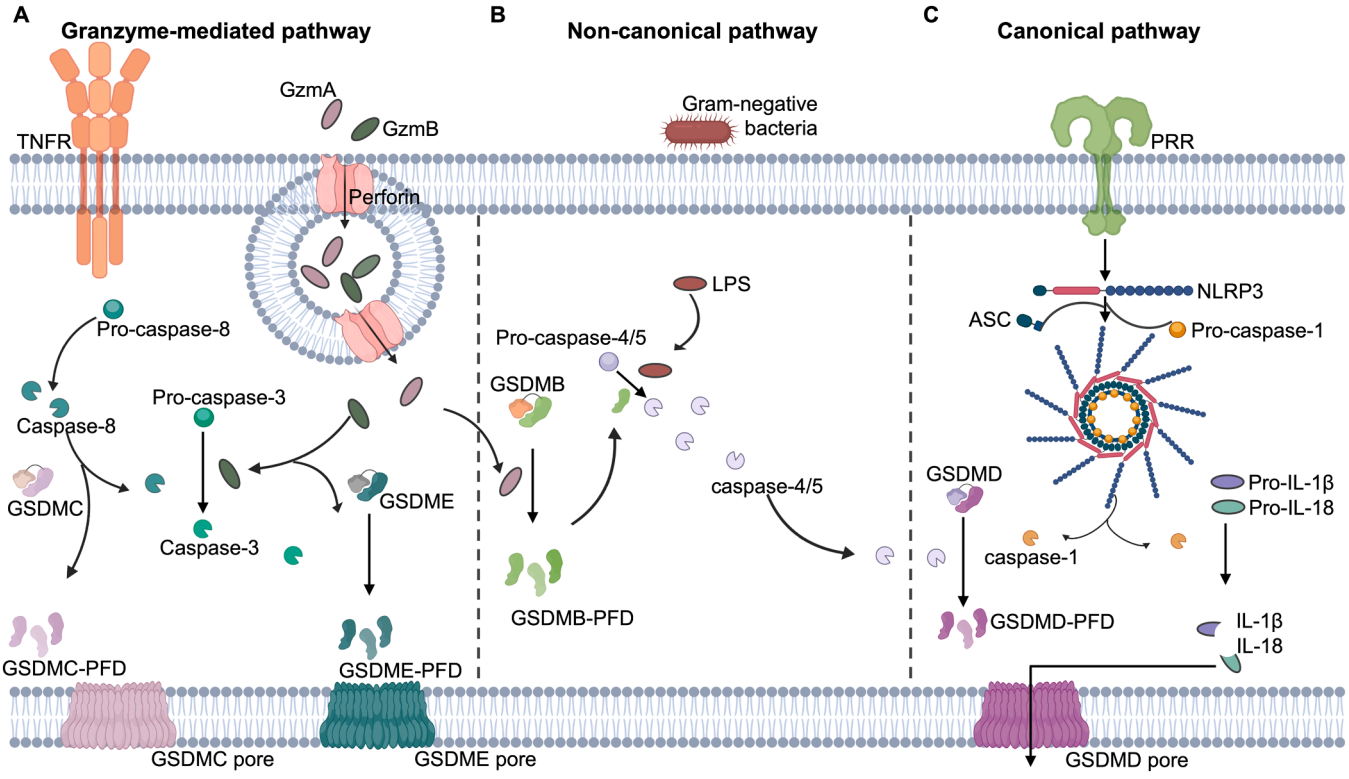

Fig. 2. Summary of several biological mechanisms involved in pyroptosis. A The mechanism of pyroptosis induced by granzymes and TNF-α/TRADD pathway. **B** Gram-negative bacteria induced cell death mediated by non-canonical pyroptotic pathways. **C** The canonical pyroptotic pathway induced by the interactions between PAMPs or DAMPs with PRRs. (Gzm A: Granzyme A; Gzm B: Granzyme B; PAMPs: pathogen-associated molecular patterns; DAMPs: damage-associated molecular patterns; PRRs: pattern recognition receptors; GSDMD-CT: GSDMD-C-terminus; and GSDME-CT: GSDME-C-terminus.).

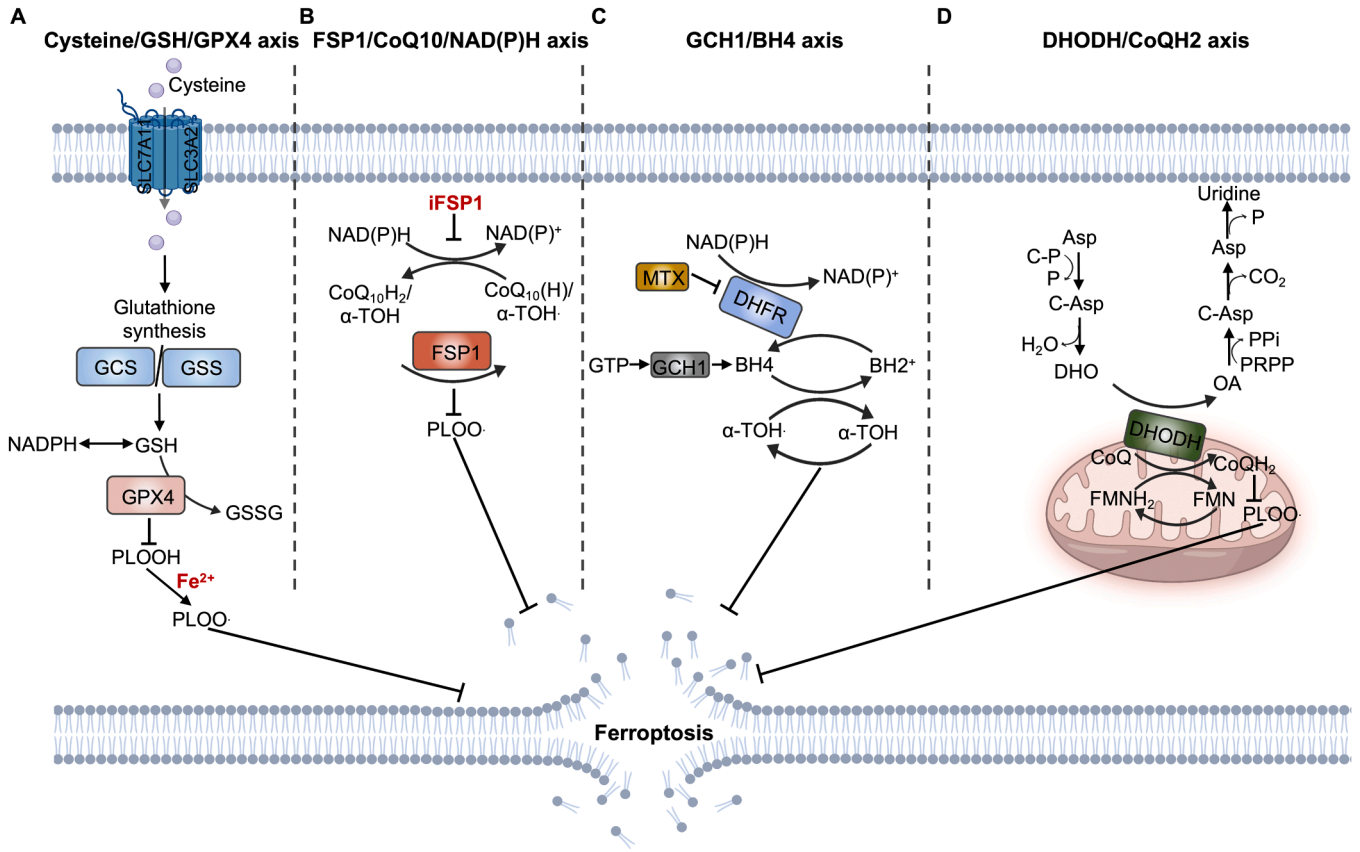

Fig. 3. Defense pathways involved in ferroptosis. A In a glutathione (GSH)-dependent manner, GPX4 selectively catalyzes the loss of oxidative activity of lipid peroxides and protects cells against the threat of ferroptosis. **B** FSP1, a phospholipid peroxidation inhibitor that does not require GSH, changes the ubiquinone on the cell membrane into reduced ubiquinol, which can prevent peroxidation and ferroptosis. **C** GCH1 protects cells from ferroptosis through the antioxidant action of BH4. **D** DHODH inhibits ferroptosis by controlling the synthesis of dihydroubiquinone in the inner membrane of mitochondria.

Current and future therapies targeting different RCD pathways in BC

Methods for bypassing the apoptotic signaling pathways that result in the death of cancer cells have drawn considerable interest for their potential application in anticancer therapy. We therefore discuss potential drugs and other agents targeting novel cell death pathways that may be applied in BC treatment (Table 1).

Potential drugs inducing novel RCD pathways

Recent studies have found that numerous currently approved drugs have powerful anticancer effects via inducing RCD modalities in clinical trials. For instance, Jin et al. demonstrated the potential of Smac-mimic LCL161 as a therapeutic agent for inducing several forms of RCD, including necroptosis in BC [49]. Then, a neoadjuvant trial provides evidence supporting the utility of LCL161 in TNBC but also highlights the toxicity risk. Therefore, before introducing the novel targeted agent LCL161 in BC therapy, we need to carefully balance toxicity and early discontinuation rate with increased pathological complete response (pCR) [50]. Koo et al. found that hypomethylating agents restore RIP3 expression and thereby promote chemotherapeutic sensitivity in BC cells, suggesting that RIP3-deficient BC patients may benefit from receiving hypomethylating medications (such as 5-azacitidine and decitabine) to promote RIP3 expression prior to conventional chemotherapy [51]. A multicenter phase II trial of 5-azacitidine and another epigenetic therapy in women with hormone-resistant BC showed that they did not meet the primary endpoint but were well tolerated, indicating that the clinical application of hypomethylating medications needs further study. At present, a good deal of necroptosis-related drugs are in the experimental stage, and bringing these drugs into the clinic is still a long way off. For example, in a study by Zhang et al., it was discovered that DHQ3, a non-benzoquinone analog of geldanamycin, increases the expression of RIPK1 and RIPK3 to induce necroptosis in TNBC cell lines [52]. Recently, it was discovered that metal-based medications induce necroptosis in the population of cancer stem cells (CSCs). According to Novohradsky et al., osmium (II)- and ruthenium (II)-p-cymene complexes with bathophenanthroline and dichloroacetate ligands (Os (II) and Ru (II) complexes) could induce necroptosis in breast CSCs [53]. In addition, a number of nickel (II) complexes with phenanthroline and dithiocarbamate ligands (Ni (II) complexes) could kill breast CSCs at low concentrations [54].

Metformin prevents the proliferation of BC cells by causing mitochondrial malfunction, which results in pyroptotic cell death. In particular, metformin is a sensitizer that boosts AMPK/SIRT1/NF-κB signaling to cause caspase-3 activation and the production of GSDME-PFD [55]. While Lu Wang and colleagues found that metformin triggers the pyroptotic death of esophageal squamous cell carcinoma cells via targeting the miR-497/PELP1 axis [56]. Furthermore, several epidemiologic studies and randomized multicenter clinical trials (such as the METTEN trial, ALTTO trial, and CCTG MA.32 trial) have successfully proved the efficacy, tolerability, and safety of adding metformin to BC patients. Therefore, antidiabetic metformin is expected to be a bona fide anti-BC metabolic therapeutic [57]. An omega-3 fatty acid called docosahexaenoic acid (DHA) has been established as an anticancer modality. Pizato et al. discovered that DHA-treated breast cancer cells produce more caspase-1 and GSDMD activation, translocate HMGB1 towards the cytoplasm, and form membrane pores, suggesting

Table 1
Summary of agents targeting novel RCD in BC.

Classification	Compound	RCD Pathway	Mechanism	References
Potential drug	LCL161	Necroptosis induction	Antagonizes with the inhibitor of apoptosis protein (IAP)	[49]
Potential drug	5-azacitidine	Necroptosis induction	Promote RIP3 expression	[51]
Potential drug	DHQ3	Necroptosis induction	Increases the activity of RIPK1 and RIPK3	[52]
Potential drug	Os (II) and Ru (II) complexes	Necroptosis induction	Targets cancer stem cells	[53]
Potential drug	Ni (II) complexes	Necroptosis induction	Targets cancer stem cells	[54]
Potential drug	Metformin	Pyroptosis induction	Boosts AMPK/SIRT1/NF-B signaling	[55]
Potential drug	DHA	Pyroptosis induction	Increases production of caspase-1	[58]
Potential drug	Tetraarsenic hexoxide	Pyroptosis induction	Inhibits phosphorylation of STAT3	[60]
Potential drug	Nobiletin	Pyroptosis induction	Targets miR-200b/JAZF1/NF-κB axis	[61]
Potential drug	Triclabendazole	Pyroptosis induction	Enhances ROS/JNK/Bax axis	[62]
Potential drug	SSD	Pyroptosis induction	Activates ROS-induced inflammasome	[63]
Potential drug	Neratinib	Ferroptosis induction	Increases intracellular iron	[64]
Potential drug	Danshen	Ferroptosis induction	Inhibits GPX4 levels	[66]
Potential drug	Ferroptocide	Ferroptosis induction	Targets the thioredoxin inhibitor	[67]
Potential drug	Ungeremine	Ferroptosis induction	Increases ROS production	[68]
Potential drug	Siramesine	Ferroptosis induction	Blocks iron transport	[69]
Potential drug	NSA	Necroptosis inhibition	Inhibits MLKL axis	[97]
Potential drug	Dimethyl fumarate	Pyroptosis inhibition	Inactivates GSDMD	[98]
NPs	FSSN	Ferroptosis and necroptosis induction	Decreases GSH levels	[71]
NPs	LipoDDP-DCT	Pyroptosis induction	Activates the capase-3 pathway	[72]
NPs	RIG-I agonist	Pyroptosis induction	Activates the STAT1 pathway	[73]
NPs	ROS-responsive nanoreactor	Pyroptosis induction	Causes oxidative stress	[74]
NPs	SAFEs	Ferroptosis induction	Induces lipid peroxidation	[75]
NPs	SRF@FeIIITA (SFT)	Ferroptosis induction	Inhibits GPX4 activity	[76]
NPs	HSPE	Ferroptosis induction	Enhances intracellular ROS	[77]
NPs	Ferritin-containing NPs	Ferroptosis induction	Elevates ROS level	[78]
Small compound	CBL0137	Necroptosis induction	Activates activity of ZBP-1	[80]
Small compound	Bufalin	Necroptosis induction	Activates the RIP1/RIP3/PARP1 axis	[82]
Small compound	Goniothalamin	Necroptosis induction	Inducing TNF-mediated necroptosis	[83]
Small compound	AVEAF	Necroptosis induction	Generates intracellular ROS	[84]
Small compound	Quercetin	Necroptosis induction	Increases RIPK1 and RIPK3 expression	[85]
Small compound	PBP	Necroptosis induction	Activates TNF-α/TNFR1 axis	[86]
Small compound	Ivermectin	Pyroptosis induction	Activates the P2 × 4/P2 × 7-gated pannexin-1 channel	[87]
Small compound	3-acyl isoquinolin-1(2H)-one	Pyroptosis induction	Inhibits MAPK/ERK pathway	[88]
Small compound	R001	Pyroptosis induction	Inhibits STAT3 activation	[89]
Small compound	DMOCPTL	Ferroptosis induction	Ubiquitination of GPX4	[90]
Small compound	BSO	Ferroptosis induction	Blocks GSH synthesis	[91]
Small compound	Cyst(e)inase	Ferroptosis induction	Improves GSH depletion	[64]
Small compound	Anti-GSDMB antibody	Pyroptosis inhibition	Antagnizes GSDMB activity	[30]
Other methods	hUCMSCs	Pyroptosis induction	Increases expression of NLRP1 and caspase-4	[92]
Other methods	TMAO	Pyroptosis induction	Activates PERK axis	[93]
Other methods	H-FIRE	Pyroptosis induction	Changes tumor microenvironment	[94]
Other methods	Erastin@FA-exo	Ferroptosis induction	Suppresses cystine/glutamate antiporters	[95]
Other methods	LPOgener	Ferroptosis induction	Induces the Fenton reaction	[96]

DHA causes pyroptosis in breast cancer cells [58]. A randomized placebo-controlled, double-blinded phase II study in obese patients with a history of stage I-III BC studies how well DHA works in preventing recurrence in BC survivors. Although compliance was satisfactory, the results did not show any changes in the levels of prespecified biomarkers, which greatly diminishes enthusiasm for further research on DHA supplementation for BC prevention [59]. Yang et al. demonstrated that tetraarsenic hexoxide inhibits the development and metastasis of TNBC cells by inducing pyroptotic cell death. Mechanistically, the pyroptosis pathway is triggered through inhibiting phosphorylation of mitochondrial STAT3, subsequently activating the mitochondrial reactive oxygen species (ROS)-mediated caspase-3-dependent cleavage of GSDME [60]. Additionally, a portion of pyroptosis-related drugs are still in the experimental phase, which emphasizes elucidating the mechanism of these drugs in BC cells. Nobiletin, a polymethoxylated flavone present in citrus fruits, has been reported to inhibit the tumorigenesis of BC. Wang and colleagues finally found that nobiletin induces pyroptosis in BC cells via the miR-200b/JAZF1/NF-κB axis [61]. In a study conducted by Yan et al., triclabendazole, a new type of imidazole for fluke resistance approved by the FDA, has been revealed to induce GSDME-dependent pyroptosis by caspase-3 activation through enhancing the ROS/JNK/Bax apoptotic pathway [62]. Moreover, Spatholobus Suberectus Dunn (SSD, Leguminosae), named “Ji Xue Teng” in traditional Chinese medicine (TCM), has been found to possess anti-TNBC ability that relies on ROS-induced inflammasome pyroptosis in cancer cells [63].

Interestingly, some FDA-approved drugs have exhibited the ability to promote ferroptosis *in vitro* and *in vivo* models. For example, neratinib, a

potent pan-tyrosine kinase inhibitor, induces ferroptosis by increasing intracellular iron levels, which potently inhibits tumor growth and brain metastasis in HER2-positive phenotype BC. Notably, these ferroptosis inducers have entered clinical trials as anti-cancer drugs and are most likely to succeed in realizing clinical application in future BC treatment [64]. Furthermore, phytochemicals with great selectivity and minimal toxicity have been reported to induce ferroptosis in BC. So far, there are only 12 chemicals that can significantly suppress cancer cell viability and tumor growth by triggering ferroptosis. Part of these phytochemicals (including quercetin and curcumin) have been the subject of clinical trials, while the others are in experimental studies, which require further investigations [65]. For example, according to Lin et al., Danshen inhibits the expression of GPX4, triggers ferroptosis in BC cell lines, and dramatically reduces the tumor volume in the nude mouse model [66]. The thioredoxin inhibitor ferroptocide is created by the 'secondary development' of the diterpene natural substance pleuromutilin. This agent can induce ferroptosis by generating lipid peroxidation along with anti-tumor effects in BC [67]. Ungeremine can also trigger ferroptosis in BC [68]. Additionally, Ma S and colleagues identified a lysosome disruptor, siramesine, in the vitro study that, when combines with lapatinib, a tyrosine kinase inhibitor, causes the death of BC cells by blocking iron transport and triggering lipid peroxidation [69].

Nanoparticles (NPs) targeting novel RCD pathways

NPs have the potential to be very successful anticancer therapeutics due to facile cell barrier penetration and an increased possibility of effective fine-tuning. As we discussed previously, shikonin exhibits antitumor potential by inducing necroptosis in BC cell lines. Nevertheless, shikonin's clinical use has been constrained because of its poor tumor-specific accumulation, low water solubility, short duration in blood circulation, and significant risk of harmful side effects on normal tissues [70]. Therefore, Feng et al. created a FSSN based on the metal-polyphenol coordination of shikonin and Fe (III), and this FSSN not only displays higher water solubility and lower cytotoxicity than shikonin in normal cells, but it is also integrated with the function of Fe ions. In mouse BC cell lines, FSSNs effectively decrease GSH levels and cause ferroptosis and necroptosis [71]. However, there remain restrictions on realizing the clinical translation of these shikonin nanomedicines. Several vital issues need to be considered, such as quality control, biosafety, efficacy, and patient compliance.

Additionally, NPs have been designed to trigger pyroptosis and demonstrate anti-BC potential in basic scientific research. For instance, in 4T1 BC xenografts, Fan and colleagues employed tumor-targeting nanoliposomes loaded with cisplatin (LipoDDP) and DCT. Reduced tumor growth and metastatic spread are observed *in vivo* after intravenous injection of LipoDDP-DCT, which raises GSDME expression (by blocking its gene promoter hypermethylation), activates caspase-3/GSDME cleavage, and induces pyroptosis [72]. In a study by Elion et al., treatment with a synthetic RIG-I (retinoic acid-inducible gene I) agonist results in pyroptosis by activating STAT1 and the NF-κB pathway in three major BC cell subtypes, which demonstrates the therapeutic effect of RIG-I in poorly immunogenic BC [73]. In another study, Kataoka et al. also constructed a ROS-responsive nanoreactor based on polyion complex-forming vesicles by incorporating thioketal linkers into a covalently cross-linked membrane network. These ROS-responsive polyion complexes promote pyroptosis by causing oxidative stress and glucose deprivation [74]. So far, despite significant progress in the development of various strategies on pyroptosis-related NPs, there are still several challenges slowing this agent's progression to clinical trials, such as a difficult synthetic and purification process, a lack of standardized protocols for preparation, and potential immunogenicity issues in the human body.

NPs are growing as a favorable solution for the development of ferroptosis, and these emerging nanomedical therapies primarily work by: 1) inducing the Fenton reaction; 2) blocking GPX4 expression; and 3) externally controlling lipid peroxidation. Modern red blood cells called sonodynamically amplified ferroptotic red blood cells (SAFEs) can activate ferroptosis by combining ROS production and lipid peroxidation, which selectively accumulates and induces desirable anticancer effects *in vivo* in the BC mouse model [75]. Nanoparticle-induced ferroptosis can also be combined with chemodynamic therapy. Liu et al. developed a ferrous supply regeneration nanomaterial (SRF@FeIIITA (SFT)) made of Fe^{3+}, a tannic acid (TA) network-like corona, and sorafenib (SRF) nanocrystals. In response to the lysosome's acidic environment, SFT nanoparticles can release SRF to inhibit GPX4 and achieve Fe^{3+} and Fe^{2+} flow, which in turn increases the accumulation of lipid peroxides to encourage ferroptosis [76]. Additionally, heparinase-driven continuous release nanoparticles (HSPE) can increase the killing capacity of tumor cells via DOX-induced ferroptosis and effectively inhibit BC spread *in vivo* in anti-tumor assays [77]. Lapatinib/PAB@Ferrition (L/P@Ferritin) nanoparticles are prepared to target the delivery of lapatinib and PAB to BC cells. Results *in vitro* and *in vivo* demonstrated a higher tumor suppression efficiency of L/P@Ferritin, accompanied by elevated levels of ROS [78].

It is worth mentioning that most of the above-mentioned NPs require their uptake by BC cells to exert their potential anti-tumor ability. Thus, the therapeutic potential of these agents has been largely limited by their tumor penetration and cellular uptake efficiency. Limitations of NPs in clinical use are also associated with, for example, immune system impact, tissue toxicity, and nanoformulation complexity. A recent study revealed by Korangath et al. has shown that starch-coated iron oxide nanoparticles (IONPs) can inhibit primary tumor growth, suppress metastases, and extend survival, even when little IONP is retained within the BC. Mechanistically, they indicated that IONPs were taken and processed by the phagocytic cells, and this can activate the TLR3 cascade, thereby inducing type-1 interferon release, T cell stimulation, and BC suppression [79]. This finding inferred that while most NPs-based cancer therapy depends on its intratumor accumulation, a strategy to treat metastatic BC by modulating host immunity via the immunogenic properties of NPs is extremely attractive. On the other hand, since some formulations of iron oxide NPs can activate T cells, it hints that potential immunogenicity issues are one of the most important factors hindering therapeutic NPs progress to clinical trials. However, research on the association between RCD-related NPs and anti-tumor immune responses is still lacking and needs to be further studied.

Small compound targeting novel RCD pathways

An increasing number of small compounds are being investigated to target the necroptotic cell death pathway in BC. For instance, the small-molecule compound CBL0137 directly activates ZBP1-dependent necroptosis, which significantly reverses the inability of BC models to respond to cancer treatments [80]. Results of a completed phase I trial showed that CBL0137 administered intravenously is generally well tolerated and has efficacy in adults with treatment-refractory solid tumors, including colorectal, prostate, and others. Thus, CBL0137 is an attractive new therapy for BC [81]. Phytochemicals have long been effective partners in the fight against several cancers. Notably, some of these natural compounds have proven to act as anti-tumoral molecules by inducing necroptosis in BC cells. Li et al. found that bufalin, an essential ingredient of the Chinese medicine Chan Su, induces necroptosis in BC by enhancing the oxygen species-mediated RIP1/-RIP3/PARP-1 pathway activation and thus inhibiting BC tumorigenesis *in vitro* and *in vivo* [82]. Khaw-On et al. found that the chemical compound goniothalamin kills malignant BC cells by inducing TNF-mediated necroptosis [83]. The alysicarpus vaginalis ethyl acetate fraction (AVEAF) shows antitumor effects by generating intracellular ROS to trigger mitochondrial-mediated intrinsic pathways and promote MCF7 cell apoptosis and necroptosis [84]. Quercetin, one of the most abundant naturally occurring flavonoids, has been discovered to be effective against a variety of cancer cells. In a study on MCF-7 cells,

Khorsandi et al. found quercetin-induced cell death by both apoptosis and necroptosis, and they noticed that the aforementioned compound causes MCF-7 cells to express more molecules like RIPK1 and RIPK3 [85]. Additionally, we demonstrated that protein-bound polysaccharides (PBP), natural compounds derived from Chinese fungus coriolus versicolor (CV), induce necroptosis in BC cells by activating the TNF- α/TNFR1 pathway [86].

Dobrin et al. found that ivermectin causes pyroptosis in TNBC cells by activating the P2 × 4/P2 × 7-gated pannexin-1 channel [87]. The ongoing phase I/II trial has been designed to test the safety and efficacy of the combination of ivermectin and balstilimab in BC patients, suggesting which exerts anticancer potential in clinical applications. Additionally, the literature precedent disclosed that 3-acyl isoquinolin-1 (2H)-ones and analogues have an anti-tumor effect in BC cells via inhibiting the MAPK/ERK pathway. Lei Ma and colleagues then found that this compound induces G2 phase arrest of the cell cycle and GSDME-mediated pyroptosis in BC cells without significantly harming human normal mammary epithelial cells [88]. Furthermore, the hirsutinolide natural product R001 has the potential to modulate multiple targets at low concentrations. Hence, this compound is less toxic and has more positive therapeutic effects overall. A recent study indicated that TNBC cells with constitutively active STAT3 are preferentially more sensitive to R001 than normal cells, which causes early oxidative stress and pyroptosis and late DNA damage, cell cycle arrest, and tumor suppression in BC [89].

As research has progressed, a growing number of *in vitro* and *in vivo* studies have shown that small-molecule substances are crucial for inducing ferroptosis in BC. Ding et al. discovered that DMOCPTL, a derivative of natural parthenolide, exhibits the anti-BC effect by inducing ferroptosis through ubiquitination of GPX4 protein [90]. Additionally, buthionine sulfoxime (BSO), a ferroptosis inducer that directly blocks the synthesis of GSH, can decrease the growth of mouse breast tumors [91]. With the deepening of research, an improved human cystathionine glyase (CGL), coined cyst(e)inase, has developed to degrade cysteine and cystine as a genetic method to improve the efficiency of GSH depletion. This method prolongs mice's longevity and suppresses the growth of BC xenografts [64].

Other methods targeting novel RCD pathways

Human umbilical cord mesenchymal stem cells (hUCMSCs) have lately been recognized as a promising cancer treatment due to their low immunogenicity and high multiplication capacity. Following the overexpression of NLRP1 and caspase-4 in the MCF-7 BC cell line, hUCMSCs induce pyroptosis in BC cells, however, hUCMSCs treatment has no effect on the cell cycle. Furthermore, a recent study discovered that clostridiales are abundant in the activated antitumor microenvironment of TNBC [92]. Interestingly, trimethylamine N-oxide (TMAO), a metabolite produced by clostridiales, has an intriguing correlation with increased immunotherapy effectiveness in the clinical cohort. Mechanistically, TMAO triggers GSDME-mediated pyroptosis in cancer cells and improves $CD8^+$ T cell-mediated antitumor immunity *in vivo* via activating the endoplasmic reticulum (ER) stress kinase PERK [93]. In a mouse 4T1 BC model, Ringel-Scaia et al. demonstrated that high-frequency irreversible electroporation (H-FIRE) is an effective tumor ablation technique. H-FIRE also has the ability to stimulate the innate immune system by dramatically inducing pyroptosis *in situ*, thereby leading to the elimination of primary tumors *in vitro* and *in vivo* [94]. Additionally, exosomes are becoming more popular as drug delivery systems because of their great biocompatibility, minimal immunogenicity, and high efficacy. Yu et al. created a formulation of erastin-loaded exosomes labeled with folate (FA) to develop FA-vectorized exosomes loaded with erastin (erastin@FA-exo), which has an inhibitory effect on the progression of BC cells by promoting ferroptosis and overcomes the drawbacks (including renal toxicity and poor water solubility) of erastin [95]. Yu et al. created LPOgeners using intact ferric ammonium citrate (FAC) and phosphatidylcholine enriched in unsaturated lipids to generate liposomes containing FAC. At high GSH levels, the Fe^{3+} encapsulated in the LPOgener is effectively reduced, which could cause lipid peroxidation to trigger the Fenton reaction-dependent ferroptosis. Due to their outstanding anticancer therapeutic efficacy and nearly non-existent systemic toxicity, LPOgeners are effective inducers of ferroptosis and can be employed in BC treatment [96].

Agents inhibiting novel RCD pathways

Necroptosis is partially tumorigenic because the underlying inflammation of necroptosis may encourage tumor growth by promoting cell proliferation, metastasis, genomic instability, and angiogenesis. Liu et al. found that the MLKL inhibitor necrosulphonamide (NSA) significantly delays tumor growth in the mouse xenograft model, which is compelling proof that necroptosis has a protumorigenic role. The absence of MLKL in MVT1 BC cells significantly inhibits the metastasis of BC to the lung [97].

Due to the dual function that pyroptosis plays in cancer, the use of pyroptosis inhibitors holds great promise for future research. According to a 2019 study, the delivery of the anti-GSDMB antibody in biocompatible nanocapsules dramatically reduced the metastasis and medication resistance of HER2 BC cells [30]. Additionally, dimethyl fumarate is a GSDMD-inactivating pyroptotic cell death inhibitor [98].

Finally, to help visualize the multiple modes of action, we displayed the modulators involved in three RCDs in BC (Fig. 4).

Mathematical models for predicting RCD signaling pathways

To sum up, studies on therapeutic agents targeting various RCD pathways mostly remain in the basic experimental stage, suggesting that further characterization of complex molecular networks of cell death regulation can help realize these BC-related therapeutic protocols through clinical trials and applied to clinical practice. Mathematical modeling is a potent tool that enables the connection between molecular biology and cell physiology by associating the qualitative and quantitative characteristics of dynamical molecular networks. This systems-oriented approach has been successfully applied to quantitatively characterize RCD signaling networks [99]. For instance, Xu et al. have developed a computational model of the necroptosis signaling pathway to investigate the necroptosis dynamics that cause cell death in the form of oscillation-induced trigger waves [100]. A more recent, detailed mathematical model of TNF-mediated necroptosis has been developed and successfully applied to explain the dynamics of necroptosis by Ildefonso et al. [101]. In addition, Zhu et al. have performed a computational study of the crosstalk between different caspase-driven pyroptosis pathways and suggest that drugs can help improve treatment protocols for cancer by switching between pyroptosis death modes [102]. Based on the former pyroptosis model, Li et al. extended the mathematical model by adding apoptosis regulation, which contributed to determining potential molecular targets for driving cancer cells into a desired death mode [103]. Konstorum et al. developed a discrete, stochastic, multistate mathematical model of ferroptosis regulation in order to investigate the sensitivity of ferroptosis induction to various signaling and perturbation conditions [104]. Therefore, precise predictive mathematical models of complex molecular networks regulating cell death can not only characterize the concrete dynamics of RCD signaling pathways but also be used to evaluate the effects of RCD modulators. More importantly, cell death *in vivo* is often characterized by their intricate interplay. The establishment of mathematical models can help comprehensively understand the interrelationship among the three forms of RCD, which is pivotal for manipulating synergistic drug combinations and developing efficient therapeutic protocols in BC.

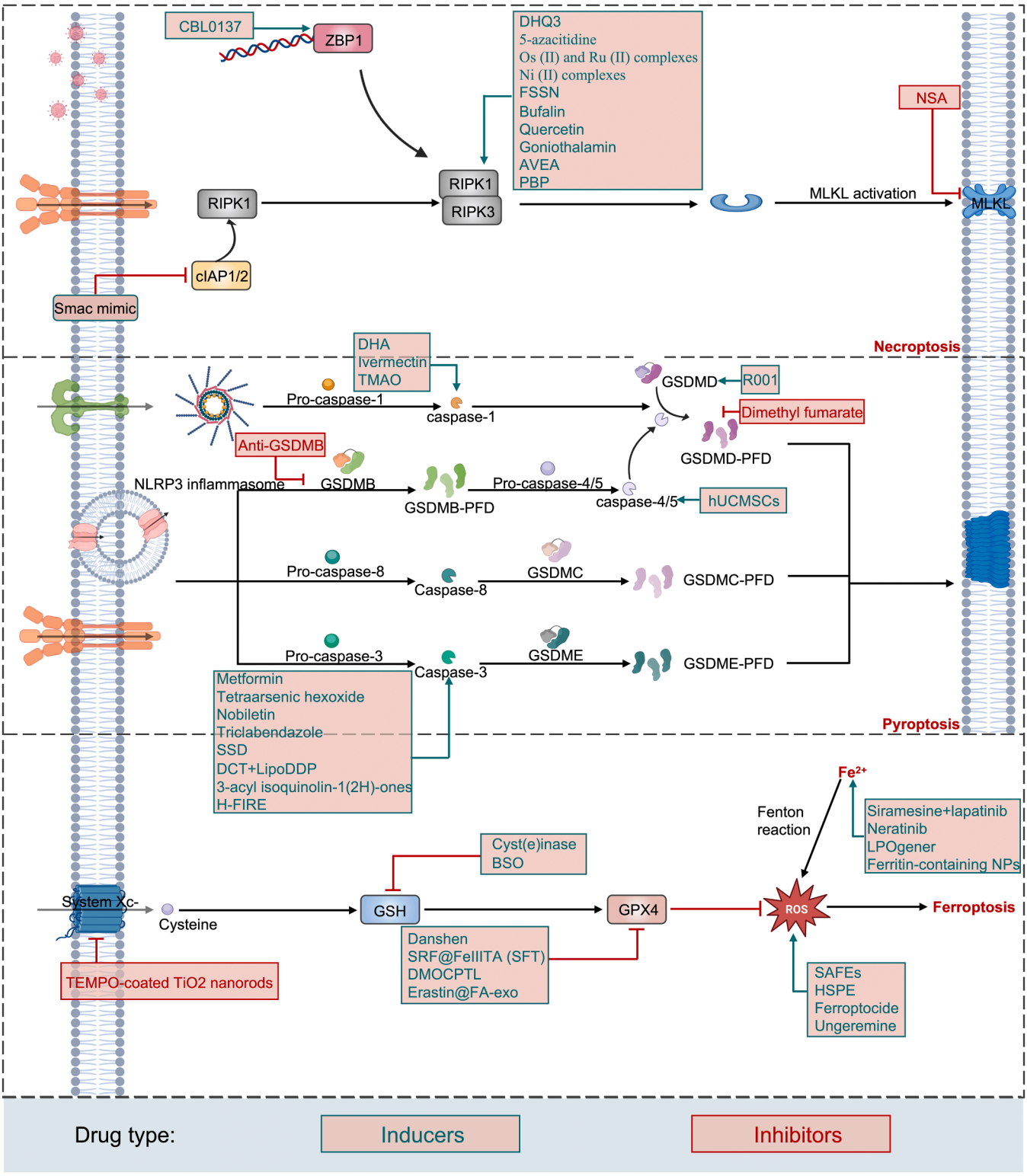

Fig. 4. Summary of novel RCD modulators involved in BC treatment.

RCD: is it a possible strategy to reverse drug resistance in BC?

Many patients with malignant BC undergo accelerated disease progression due to de novo and acquired drug resistance, which appears to be significantly influenced by apoptosis malfunction [105]. RCD pathways utilize components that are different from the apoptotic pathway, cancer cells that are resistant to apoptosis agents may be sensitive to RCD modulation. Therefore, triggering RCD pathways is a promising strategy to overcome chemoresistance in BC. Han et al. demonstrated that shikonin, a naturally occurring naphthoquinone, triggers necroptotic cell death in Bcl-2-overexpressed MCF-7 BC cells that are resistant to proapoptotic medicines [106]. TNBC cells are resistant to clinical doses of gefitinib. Inhibition of GPX4 increases gefitinib sensitivity by encouraging cell ferroptosis. Therefore, GPX4 is a promising

therapeutic target for gefitinib resistance in TNBC [107]. To overcome tumor drug resistance, a chemotherapeutic agent doxorubicin (DOX) is combined with Fe (VI) species to form DFHHP in HMS nanomaterials, which provides exogenous iron and produces highly reactive ROS by the Fenton reaction, depletion of GSH, and exacerbating ferroptosis in BC cells [108]. Additionally, DOX can also be coupled with the ferroptosis inducer ferric chloride (FeCl3) and the superoxide dismutase (SOD) activator tannic acid (TA) to synthesize a drug-organic-inorganic self--assembled nanosystem (DFTA), which effectively inhibits the progression of ER-positive BC cells by activating a cascade ferroptosis reaction [109]. However, take shikonin as an example. The combination of RCD modulators with chemotherapy may obviously enhance the toxic side effects of BC treatments. It is imperative to further develop highly effective and less toxic RCD-inducing drugs, which have more potential to surmount treatment resistance in BC.

Discussion

The current literature suggests that the relationship between regulated cell death (RCD) and the occurrence and development of breast cancer (BC) and strategies aimed at RCD modalities are complicated, but these challenges additionally provide novel and exciting treatment options, and how to bring these novel therapeutic modalities to the clinic will be the focus of our follow-up research. In this review, we summarized the molecular mechanisms of three newly raised subroutines of RCD in BC, including necroptosis, pyroptosis, and ferroptosis. Blocking necroptosis by RIPK1/3 and MLKL deletion in BC dramatically promotes tumor development and metastasis. Pyroptosis exerts a potent effect on activating anti-tumor immunity, which may offer innovative solutions for BC immunotherapy. Multiple ferroptosis-associated regulators are independent prognostic factors in BC. In recent years, in order to reduce the risk of tumor progression, promote individualized treatment of BC, and decrease the toxicity of tumor treatment, researchers have done a lot of research about RCD modulators in BC therapy. We complement the review of 13 potential agents treating BC by mainly targeting necroptosis, 17 potential agents treating BC by mainly targeting pyroptosis, and 15 potential agents treating BC by mainly targeting ferroptosis. Escape from apoptosis often leads to drug resistance in tumors. We summarize four potential agents for improving the chemosensitivity of BC by targeting RCD. Of note, considering the types of cancer cells and the use of chemotherapy or immunotherapy, either alone or in combination, it is important to investigate the internal relationships and coordination mechanisms between various types of RCD. We recommend establishing predictive mathematical models in order to evaluate the effects of these RCD modulators and achieve synergistic drug combinations for overcoming drug resistance in BC.

Nevertheless, compared with the issues that have been resolved, there are still some additional mysteries that need to be answered before the practical application. Firstly, it is challenging to figure out whether the ability to reverse drug resistance by RCD inducers is universal or limited to a small subset of BC cells with certain characteristics. We need to identify a suitable target population that will most likely profit from this strategy, given that the sensitivity to RCD inducers varies greatly among multiple subtypes of BC cells. Additionally, like the combination of RCD inducers with chemotherapy, is there any likelihood of achieving synergistic effects by combining endocrine therapy and HER2-targeted therapy with RCD in the treatment of BC? Deeper insight into the mechanisms of RCD will contribute to this goal. Secondly, RCD has been linked to multiple disorders in BC patients, such as ischemia illnesses and degenerative diseases. It will be crucial to create specialized medications targeting RCD in cancer cells while minimizing systemic adverse effects. In this respect, we expect that future preclinical and clinical trials will be done to examine the application of novel RCD modulators in cancer patients. Last but not least, long-term regulation of a single RCD subroutine often leads to drug resistance, so it is essential to explore any additional medications that efficiently target several RCD subroutines and will be applied clinically. A number of concerns must be resolved before RCD is formally applied in clinical settings.

Availability of data and materials

Not applicable.

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CRediT authorship contribution statement

Bifei Fu: Writing – original draft, Conceptualization, Writing – review & editing. **YuMing Lou:** Writing – original draft, Validation, Writing – review & editing. **Pu Wu:** Data curation, Writing – review & editing. **Xiaofeng Lu:** Writing – review & editing, Supervision, Conceptualization. **Chaoyang Xu:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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