Revolutionizing breast cancer treatment: Harnessing the related mechanisms and drugs for regulated cell death (Review)

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Abstract. Breast cancer arises from the malignant transformation of mammary epithelial cells under the influence of various carcinogenic factors, leading to a gradual increase in its prevalence. This disease has become the leading cause of mortality among female malignancies, posing a significant threat to the health of women. The timely identification of breast cancer remains challenging, often resulting in diagnosis at the advanced stages of the disease. Conventional therapeutic approaches, such as surgical excision, chemotherapy and radiotherapy, exhibit limited efficacy in controlling the progression and metastasis of the disease. Regulated cell death (RCD), a process essential for physiological tissue cell renewal, occurs within the body independently of external influences. In the context of cancer, research on RCD primarily focuses on cuproptosis, ferroptosis and pyroptosis. Mounting evidence suggests a marked association between these specific forms of RCD, and the onset and progression of breast cancer. For example, a cuproptosis vector can effectively bind copper ions to induce cuproptosis in breast cancer cells, thereby hindering their proliferation. Additionally, the expression of ferroptosis-related genes can enhance the sensitivity of breast cancer cells to chemotherapy. Likewise, pyroptosis-related proteins not only participate in pyroptosis, but also regulate the tumor microenvironment, ultimately leading to the death of breast cancer cells. The present review discusses the unique regulatory mechanisms of cuproptosis, ferroptosis and pyroptosis in breast cancer, and the mechanisms through which they are affected by conventional cancer drugs. Furthermore, it provides a comprehensive overview of the significance of these forms of RCD in modulating the efficacy of chemotherapy and highlights their shared characteristics. This knowledge may provide novel avenues for both clinical interventions and fundamental research in the context of breast cancer.

Contents

1. Introduction

Breast cancer, a malignancy arising from the epithelial cells of the breast, has witnessed a steady increase in incidence over the years (1). As per the 2020 Global Cancer Statistics Report published in CA: A Cancer Journal for Clinicians, breast cancer surpassed lung cancer to become the world's most prevalent type of cancer in 2020 (2). In that year, an estimated 2.3 million new breast cancer cases were diagnosed, representing 11.7% of all global cancer cases, and 685,000 individuals succumbed to the disease, accounting for 6.9% of global cancer-related deaths (2). Among the types of cancer affecting females, breast cancer stands out with a quarter of the incidence rate and a sixth of the mortality rate, ranking first in terms of incidence in 159 countries and mortality in

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110 countries (2). The mainstay of treatment for breast cancer is surgical excision, radiotherapy and adjuvant targeted therapies; however, clinical studies have found that the long-term use of this treatment does not improve patient survival (3). In light of these findings, regulated cell death (RCD) has emerged as a promising avenue for both breast cancer prevention and treatment strategies.

In 2018, the Cell Death Committee refined the definition of RCD by emphasizing its process mechanisms and updating the classification system (4). RCD encompasses a diverse array of developmental and immunological pathways that culminate in distinct modes of cell demise, resulting in varied morphological transformations and immunological consequences (5). This type of cell death can occur intrinsically, without the interference of external factors, serving as an inherent component of physiological programs, such as development or tissue renewal (6,7). This entirely physiological form of RCD is often referred to as programmed cell death. However, RCD can also arise from disruptions in the intracellular or extracellular microenvironment when these disturbances are too severe or prolonged, exceeding the capacity of adaptive responses to maintain cellular homeostasis (8). Oxidative stress, characterized by the generation of reactive oxygen species (ROS), has been implicated as a potential trigger for various forms of RCD. The production of ROS and the effectiveness of antioxidant defenses are reportedly influenced by the surrounding environment (5). In recent years, research on RCD in cancer has increasingly focused on modes, such as cuproptosis, ferroptosis, pyroptosis, immunogenic cell death and autosis. Therefore, the present review primarily discusses and summarizes the regulatory mechanisms, relevant genes and potential drugs associated with cuproptosis, ferroptosis, pyroptosis and other such modes of RCD in the context of breast cancer.

2. Cuproptosis and breast cancer

Copper (symbol, Cu) serves as an essential cofactor for all living organisms, with intracellular levels meticulously maintained within a narrow range. It plays a pivotal role in various physiological processes, including mitochondrial respiration, antioxidant activity and macromolecular biosynthesis. However, exceeding the threshold of homeostatic mechanisms can induce detrimental effects, regardless of whether copper levels are deficient or excessive (9-11). Cuproptosis, a recently discovered cell death pathway, arises specifically from copper overload and operates independently of other known death mechanisms. Copper ions directly bind to lipoproteins within the tricarboxylic acid cycle (TCA) metabolic pathway, causing anomalous aggregation and interfering with the iron-sulfur cluster scaffold protein in the respiratory complex. This disruption culminates in a proteotoxic stress response, ultimately leading to cell death (12-15).

Cuproptosis is distinguished from other types of RCD. Cuproptosis, a unique form of RCD, is specifically induced by copper ion carriers. Notably, inhibitors targeting known cell death pathways, including ferroptosis, necrosis, apoptosis and oxidative stress, exhibit a limited ability to prevent copper ion carrier-induced cell death. This distinct mechanism significantly differentiates cuproptosis from traditional modes of cell death, such as apoptosis and necroptosis. Mitochondrial respiration plays a crucial role in the regulation of cuproptosis. Treatment with mitochondrial antioxidants, fatty acids and inhibitors of mitochondrial function significantly influences copper ion carrier sensitivity, suggesting dependence on mitochondrial activity rather than adenosine triphosphate (ATP) production (16). Key genes contributing to copper-induced death include *FDX1* and six genes involved in protein S-acylation, all essential for mitochondrial aerobic metabolism. The knockdown of *FDX1* (encoding a protein converting divalent copper ions to toxic monovalent forms) and six lipoylated protein genes (*LIPT1, DLD, LIAS, DLAT, PDHA1* and *PDHB*) has been shown to successfully rescue cells from copper ion-mediated death (16). *FDX1* acts as an upstream regulator of protein lipoylation, a conserved lysine post-translational modification limited to four enzymes within metabolic complexes regulating carbon entry into the TCA cycle. It has been established that copper directly binds and induces the oligomerization of lipoylated DLAT. Notably, *FDX1* deletion eliminates protein lipoylation, preventing copper binding by DLAT and DLST, indicating the critical role of the lipoyl moiety in copper binding. This unique death mechanism observed in cuproptosis aligns with observations in a genetic model of copper homeostasis dysregulation. Studies using a mouse model of Wilson's disease further suggest that copper overload induces cellular effects identical to those triggered by copper ion carriers, confirming the shared mechanism between copper homeostasis dysregulation and copper ion carrier-induced cell death (17).

Mechanisms involved in cuproptosis. While cuproptosis holds promise, several aspects remain enigmatic. The specific roles of key factors, such as *FDX1* require further investigation. Additionally, the mechanisms underlying cuproptosis inhibition in healthy cells are unclear. Furthermore, previous studies suggest that hte various possible cuproptosis-related mechanisms require better integration. Finally, characteristic morphological and molecular changes in cuproptosis-affected cells have not been fully described (18-20).

Copper, crucial for enzymes, necessitates meticulous control at low levels for normal physiological function. Studies highlight its role in cancer progression (21-25). Notably, patients with breast cancer exhibit significantly higher serum levels of copper compared to the controls, suggesting its potential in early detection and monitoring. In triple-negative breast cancer (TNBC), inhibiting mitochondrial copper forces tumor cells to switch from respiration to glycolysis, reducing energy production and ultimately hindering tumor growth and improving prognosis (26-30). The novel concept of cuproptosis sheds light on the copper-cancer link. Elesclomol, a copper ion carrier, binds to environmental copper and delivers it into cells, triggering cell death. This approach may be most effective in cancers highly expressing mitochondrial lipoylated proteins and relying heavily on respiration. Moreover, it could be particularly useful in apoptosis-resistant cancers, providing a novel strategy with which to eliminate cancer cells by leveraging the unique properties of copper (31,32). Building upon the anticancer properties of copper, chelators and carriers are currently undergoing preclinical and clinical evaluations in various tumor types. Copper chelation therapies, such as

tetrathiomolybdate and ATN-224 have reached phase II clinical trials in breast cancer. Disulfiram, a copper ion carrier, is under phase II investigation for malignant glioma, while elesclomol holds promise for the treatment of melanoma in phase II trials (33-36).

Relevant targets for cuproptosis in breast cancer. Intracellular copper overload has recently been linked to a novel form of cell death known as cuproptosis. Independent of traditional pathways, cuproptosis does not activate caspase-3 and remains unaffected by apoptosis inhibitors (15). Genes associated with this process include *FDX1, LIPT1, LIAS, DLD, DBT, GCSH, DLST, DLAT, PDHA1, PDHB, SLC31A1, ATP7A* and *ATP7B*. These genes primarily regulate processes, such as glycolysis, the TCA cycle, and steroid and vitamin D metabolism. Notably, SLC31A1 facilitates copper uptake, while ATP7A and ATP7B are responsible for copper efflux, maintaining intracellular copper levels (37-41). The overexpression of SLC31A1 and the deletion of ATP7B can increase susceptibility to cuproptosis, whereas the knockdown of nine specific genes (*FDX1, LIAS, LIPT1, DLD, DLAT, PDHA1, PDHB, GCSH* and *DBT*) confers resistance (15). While the role of copper in breast cancer, particularly its impact on the immune microenvironment and immunotherapy, has been well-established (42), the association between seven key cuproptosis-associated genes and breast cancer remains unexplored. These genes include *PGK1* (mitochondrial metabolism and tumorigenesis), SLC family members *SLC52A2* and *SLC16A6* (metabolic transport), *SEC14L2* (vitamin E uptake), *RAD23B* (nucleotide excision repair and apoptosis), *CCL5* (inflammatory cell migration) and *MAL2* (transcytosis in hepatocellular carcinoma) (43-58).

Song *et al* (59) analyzed the protein expression of the cuproptosis-related genes, *FDX1*, *LIPT1, MTF1, DLD, DLAT, PDHA1* and *PDHB*, in breast cancer tissues and their mRNA expression in cuproposis-inducible breast cancer cell models. Notably, RAD23B expression was found to be positively associated with breast cancer progression, drug resistance and a poor prognosis of patients with breast cancer. Notably, both PD1 and PDL1 expression exhibited a positive correlation with RAD23B expression, suggesting that patients with higher RAD23B levels may be more responsive to immune checkpoint blockade therapy targeting the programmed cell death 1 (PD-1)/PD-L1 axis (59).

Recent advances in cuproptosis-related drugs. In addition, the crucial role of cuproptosis in tumor cells presents an opportunity to develop novel anticancer drugs. One such example is the platelet vesicle (PV)-coated cuprous oxide nanoparticle (Cu_2O)/TBP-2 cuproptosis sensitization system (PTC). Modified by AIE photosensitizer (TBP-2), Cu_2O and PV mimicry, PTC can enhance its long-term blood circulation and tumor targeting ability. Subsequently, PTC is rapidly degraded to release copper ions under acidic conditions and hydrogen peroxide in tumor cells. Under light irradiation, TBP-2 rapidly enters the cell membrane and generates hydroxyl radicals to consume glutathione and inhibit copper efflux. Accumulated copper can cause lipoylated protein aggregation and iron-sulfur protein loss, which result in proteotoxic stress and ultimately, in cuproptosis. PTC inhibits tumor cell proliferation and invasion through cuproptosis. Notably, PTC research, primarily in patients with lung metastases from breast cancer, have shown the significant inhibition of metastatic tumor cell growth and multiplication in the lungs (60). Furthermore, the hyaluronic acid-dopamine (HD)/berberine hydrochloride (BER)/glucose oxidase (GOx)/Cu hydrogel reactor system provides a promising avenue for multiple breast cancer treatments. This system effectively inhibits tumor growth through a combination of approaches: GOx and copper sulfate convert accumulated glucose into hydroxyl radicals within tumor cells, enacting starvation/chemokinetic therapy. Additionally, Cu induces cuproptosis, further hindering tumor cell growth. BER, included as a chemotherapeutic agent, synergizes with the starvation/chemokinetic/cuproptosis modalities. This 'hydrogel multiplicity effect' allows the system to potentially reduce the size of breast cancer pre-operatively, facilitating surgical resection (61). While these novel drugs harness cuproptosis for therapeutic purposes, their clinical efficacy remains to be determined as they are currently limited to biological experiments. However, their potential offers hope for future advancements in breast cancer treatment.

3. Ferroptosis and breast cancer

Ferroptosis proposed by Dixon *et al* (62) in 2012, is a unique form of cell death distinct from apoptosis and necrosis, triggered by a compound known as RSL3 (62). It is characterized by the iron-dependent accumulation of lipid peroxidation to lethal levels, affecting cellular structures and metabolism. This includes mitochondrial atrophy, increased membrane density, disrupted membrane integrity and the depletion of intracellular NADH (63). Three key mechanisms drive ferroptosis: i) Transferrin and L-glutaminase regulation in cancer cells (64); ii) the depletion of glutathione, leading to glutathione peroxidase 4 (GPX4) inactivation (a core antioxidant enzyme) and the subsequent disruption of the antioxidant system in cancer cells (65); and iii) the peroxidation of unsaturated fatty acids in cell membranes by divalent iron or esterases in cancer cells (66).

Ferroptosis targets in breast cancer. The mammary gland specifically regulates ferroptosis, a type of RCD. Adipocytes, fat cells in the mammary gland, significantly influence breast cancer cell growth, and promote migration and invasion. In breast cancers expressing the *ACSL3* gene, adipocytes protect cancer cells from ferroptosis by providing oleic acid, creating a unique tumor microenvironment (67-69). Hypercholesterolemia, high blood cholesterol, promotes breast cancer development and metastasis by resisting ferroptosis directly or through its metabolite, 27-hydroxycholesterol (70,71). When treated with statins, cancer cells may increase their uptake of exogenous cholesterol or boost their cholesterol production, highlighting the need for real-time tumor monitoring in patients with breast cancer taking statins (72). Ferroptosis holds significant relevance to breast cancer, offering potential for clinical screening and prognosis. Sha *et al* (73) identified the expression of ACSL4, a positive regulator of ferroptosis, as an independent predictor of the pathological complete response to neoadjuvant chemotherapy, with a higher expression suggesting a greater sensitivity.

Studies have also shown that GPX4, an antioxidant enzyme, regulates mitochondria-mediated apoptosis in cancer cells through the modulation of EGR1, functioning as a tumor suppressor in well-differentiated breast cancers and potentially serving as a therapeutic target (74). Zhang *et al* (75) identified long non-coding RNAs (lncRNAs) closely related to ferroptosis through Cox regression analysis, which can accurately predict the prognosis of patients with breast cancer. These lncRNAs, as characteristic molecules of pyroptosis (another form of RCD), may play a role in antitumor immune processes and hold potential as therapeutic targets (76). Current evidence suggests that MTHFD2, a mitochondrial enzyme involved in folate metabolism, is highly expressed in embryos and various tumors. As a potential regulator of ferroptosis in breast cancer, it may serve as a crucial molecular biomarker and a novel therapeutic target for predicting the prognosis of patients with TNBC (77,78). Furthermore, Yadav *et al* (79) found that breast cancer cells can evade cell death by overexpressing SLC7A11, which resists ferroptosis by influencing the tumor microenvironment. Notably, miR-5096 can target and downregulate SLC7A11, inducing ferroptosis in breast cancer cells and inhibiting tumor growth (79-81). Zhang *et al* (82) constructed a nomogram based on nine ferroptosis-related genes. These ferroptosis-related genes were significantly associated with the level of immune cell infiltration in patients with breast cancer, suggesting their potential use as therapeutic targets or biomarkers (82-90). Additionally, studies have shown that the deletion of CircRHOT1 inhibits breast cancer cell proliferation and induces apoptosis, while the knockdown of CLCA2, REEP6, SPDEF and CRAT can predict breast cancer prognosis based on metabolic gene classification (91,92). Research on ferroptosis-related regulatory mechanisms and genes is ongoing, holding promise for improved breast cancer screening and treatment. It can be expected that these research findings may translate into clinical applications in the near future.

Related drugs that can induce ferroptosis. Currently, promising drug studies are investigating the potential of targeting ferroptosis, a form of cell death, in the treatment of breast cancer. Several novel drugs have been proposed that act on this pathway to enhance existing therapies. Zhang *et al* (93) constructed heparanase (HPSE)-driven sequential release nanoparticles, which consisted of β-cyclodextrin-grafted heparin [NLC/H(D + F + S) NPs] co-modified with doxorubicin (DOX), di-ferric iron (Fe^{2+}) and a TGF-β receptor inhibitor (SB431542); co-loading modification effectively enhanced intracellular ROS levels and activated the ferroptosis pathway. The increased production of ROS also triggered apoptosis, reduced an enzyme linked to tumor invasion (MMP-9) and synergized with ferroptosis for the treatment of breast cancer (93). Similarly, polydopamine nanoparticles loaded with iron and DOX exhibit a wide range of anticancer effects (94). Cinnamaldehyde dimers formulated into lipid-like materials deplete glutathione, a key antioxidant, and when combined with the anticancer drug, sorafenib, significantly enhance ferroptosis and trigger a potent immune response in mice, leading to complete tumor eradication (95,96). Erastin@FA-exo, a folic acid-labeled exosome carrying the ferroptosis inducer, erastin, inhibits the expression of GPX4, depleting intracellular glutathione and upregulating cysteine dioxygenase, leading to excessive ROS production, both hallmarks of ferroptosis. This approach effectively reduces the survival of TNBC cells *in vivo* and exhibits high biocompatibility compared to conventional erastin, potentially reducing side-effects and paving the way for improved clinical applications (97). These novel drugs offer exciting new possibilities for the clinical treatment of breast cancer by harnessing the power of ferroptosis.

Several common clinical drugs have significant inhibitory effects on breast cancer cell growth. For example, metformin reduces the protein stability of SLC7A11 by inhibiting its UFMyation process, and SLC7A11 opposes ferroptosis by affecting the tumor microenvironment to resist the ferroptosis of tumor cells, thereby inhibiting the growth of breast cancer cells (81,82,98). Siramesine and lapatinib initially induce ferroptosis during the death process in breast cancer cells, but this transforms into autophagy after 24 h (99). In this process, ROS production plays a key role, and cystine transport inhibition, ferroportin-1 and transferrin are involved in the induction of ferroptosis (99,100). Everolimus, a targeted therapeutic agent for breast cancer, can also undergo ferroptosis by inducing the activation of the FKBP1A/SLC3A2 axis. The specific mechanism is that its related protein, FK506-binding protein 1A (FKBP1A), binds to SLC3A2 and negatively regulates SLC3A2 expression during the everolimus-induced ferroptosis of breast cancer cells and the promotion of antiproliferative Th9 lymphocytes (101). This finding suggests that everolimus may be more effective in breast cancer patients who are more sensitive to it, potentially increasing the efficacy of chemotherapy and reducing the dose of chemotherapeutic agents needed (101). Ketamine inhibits breast cancer cell proliferation by targeting the KAT5/GPX4 axis to induce ferroptosis (73). Additionally, targeting GPX4 cann enhance the anticancer effects of gefitinib, suggesting that the study of the two drugs together may provide a new direction for clinical treatment (102,103). Simvastatin has been reported to inhibit HMGCR expression and downregulate the mevalonic acid pathway and GPX4, thereby inducing ferroptosis in TNBC cells (104). Holo lactoferrin induces ferroptosis in cancer cells and sensitizes TNBC cells to radiotherapy (105). Holo lidocaine promotes ferroptosis in ovarian and breast cancer cells via the miR-382-5p/SLC7A11 axis (106).

Some common plant extracts have also been found to exert a promoting effect on ferroptosis. For example, curcumin has been shown to significantly downregulate GPX4 and upregulate HO-1, and both HO-1 and GPX4 enhance ferroptosis in breast cancer (71,72,107). Red ginseng polysaccharides, an effective extracted component of ginseng, also promote ferroptosis, inhibit GPX4 expression and exert antitumor effects (108). These findings suggest that ferroptosis may be a novel therapeutic target for breast cancer. DMOCPTL, a derivative of the natural product, chamomile lactone, can directly bind to GPX4 protein to induce GPX4 ubiquitination and induce ferroptosis. This substance effectively inhibits the growth of breast tumors without significant cytotoxicity, rendering it a potential treatment option for patients with TNBC (74). On the whole, the latest research findings on ferroptosis provide new hope for the development of more effective treatments for breast cancer. However, further research is required in order to develop a complete treatment plan that utilizes ferroptosis.

4. Pyroptosis and breast cancer

Pyroptosis, a novel type of RCD distinct from apoptosis, was first proposed by Cookson and Brennan (109) in 2001, as a rapid death mechanism observed in *Salmonella*-infected macrophages dependent on caspase-1 activation. Gasdermin (GSDM) proteins, the key molecules in pyroptosis, induce cell membrane lysis (110). There are two main categories of pyroptosis mechanisms: Classical and non-classical pathways. The classical pyroptosis pathway is triggered by exogenous or endogenous microbial infections that stimulate the production of inflammasomes. These inflammasomes activate caspase-1 proteins, which in turn disrupt the integrity of the cell membrane. Additionally, this pathway promotes the activation and release of the inflammatory cytokines, interleukin (IL)-1β and IL-18. The combined action of caspase-1 proteins and inflammation leads to pyroptosis (111-113). The non-classical pyroptosis pathway, on the other hand, is mediated by lipopolysaccharide-activated caspase-4/5/11 (114).

Mechanisms and genes involved in pyroptosis in breast cancer. Pyroptosis and its association with tumors have become a prominent research area in recent years, and the present review specifically summarizes the association between pyroptosis and breast cancer. Breast cancer exhibits a unique regulatory mechanism associated with pyroptosis. Mitochondrial uncoupling protein 1, linked to an production of body heat, has a high expression in breast cancer cells. This leads to mitochondrial swelling and autophagy, activating GSDME, stimulating antitumor immunity, and ultimately resulting in pyroptosis. This process inhibits breast cancer cell proliferation and holds potential as a prognostic marker (115-117). PD-L1, exhibiting nuclear transcriptional activity, participates in the pyroptosis pathway and modulates the tumor microenvironment. In breast cancer cells, this manifests as TNF-α activating caspase-8, which, in the presence of GSDMC and hypoxia-activated nPD-L1, converts apoptosis into pyroptosis, leading to tumor necrosis in hypoxic areas (118). As identified in the literature, the dysregulation of numerous pyroptosis genes is associated with breast cancer prognosis. The high expression of *CASP6, CASP5, TIRAP, SCAF11, NLRP7, PLCG1, GSDMC, GSDMD* and *NLRC4* is associated with a poor prognosis, while the high expression of *ELANE, CASP9, CASP8, GSDMB, CASP4, CASP1, TNF, NOD1, PYCARD, NLRP6, NLRP3, NLRP2, IL6, NLRP1, IL18* and *IL1B* is associated with improved outcomes (27,119-130). Furthermore, several genes emerged as potential therapeutic targets for breast cancer. *DRD2*, for instance, inhibits NF-κB signaling activation by binding to β-arrestin2, downregulating DDX5 and eEF1A2. This combined action suppresses the NF-κB signaling pathway and p65 phosphorylation. Additionally, DRD2 modulates the tumor microenvironment and promotes macrophage M1 polarization, ultimately triggering pyroptosis in breast cancer cells (131). In a previous study, *SCAF11* expression was found to be elevated in breast tumor cell lines, and its high levels were shown to be associated with a poor prognosis (120). Silencing SCAF11 using siRNA significantly reduced the proliferation and colony growth of BT549 and T47D breast cancer cell lines. GSEA analysis revealed that SCAF11 co-expressed genes were primarily involved inflammatory and immune-related pathways (131). Moreover, *SCAF11* expression exhibited a positive correlation with immune checkpoints, such as PD-L1, B7H3 and PDCD1LG2. Based on these findings, *SCAF11*, as a pyroptosis regulatory gene, warrants exploration as a potential therapeutic target for breast cancer patients (131).

Anti-breast cancer drugs that can leverage pyroptosis. Research on pyroptosis in breast cancer has led to investigations into the potential of existing drugs to induce this cell death process. DOX exhibits a three-pronged approach: It dose-dependently reduces the viability of MDA-MB-231 and T47D cells, activates caspase-3 through GSDME, induces the accumulation of intracellular ROS, and subsequently stimulates the phosphorylation of JNK and the activation of caspase-3, and culminates in pyroptosis, exerting its anticancer effects (132). Tetraarsenic arsenic hexaoxide exerts its anticancer effects by targeting a crucial factor in breast cancer cells, mitochondrial STAT3. Inhibiting its activation leads to mitochondrial ROS-mediated pyroptosis (133,134). Nigericin, derived from *Streptomyces hydrophobicus*, triggers pyroptosis in TNBC cells by inducing potassium efflux and subsequent mitochondrial ROS production. This process activates the caspase-1/GSDMD pathway. Moreover, combining nigericin with anti-PD-1 antibodies exhibits synergy in treating advanced triple-negative breast cancer (135). Notably, trimethylamine N-oxide (TMAO), a metabolite produced by the *Clostridium* genus, induces pyroptosis in tumor cells by activating the endoplasmic reticulum kinase, PERK. This, in turn, enhances CD8 T-cell-mediated antitumor immunity in TNBC models *in vivo*. As immunotherapy is a crucial option for these patients, the ability of TMAO to boost its efficacy suggests its potential application in the treatment of TNBC (136). Azurocidin-1, a protein originating from neutrophils and predominantly stored in azurophilic granules, exerts its effects on pyroptosis in TNBC cells through the regulation of the pNF-κB/NLRP3/caspase-1/GSDMD axis. The identification of Azurocidin-1 holds promise in the development of novel immunotherapeutic approaches for the treatment of TNBC (137). The treatment of breast cancer cells with docosahexaenoic acid has been found to increase the activation of caspase-1 and GSDMD, enhance the secretion of IL-1β, promote the translocaton of high-mobility group protein B1 (HMGB1) to the cytoplasm and to lead to the formation of membrane pores. These findings suggest that docosahexaenoic acid induces the pyroptosis-programmed death of breast cancer cells and exerts an anti-breast cancer effect (138). Xihuangwan, a traditional Chinese medicine, has been found to induce pyroptosis via the cyclic AMP-activated protein kinase (cAMP)/protein kinase A signaling pathway, and inhibit the proliferation, migration and invasion of breast cancer cells (139). Dihydroartemisinin, a plant extract, promotes the AIM2/caspase-3/DFNA5 axis in breast cancer cells and induces pyroptosis, inhibiting breast cancer growth (140). In addition, *Ganoderma lucidum* extract (GLE) activates cysteine 3 and further cleaves GSDME proteins to form membrane pores in cell membranes, thereby releasing large amounts of inflammatory factors in breast cancer cells, leading to pyroptosis and inhibiting the growth and multiplication of breast cancer cells. GLE also disrupts multiple steps of tumor metastasis, including adhesion,

migration, invasion, colonization and angiogenesis. Overall, GLE offers a potential approach for the treatment of breast cancer that could complement chemotherapy or immunotherapy for cancer metastasis (141).

Current research has identified a novel therapeutic molecule, a bionic nanoparticle of indocyanine green and decitabine, which synergistically upregulates GSDME expression through DNA methylation inhibition and enhances caspase-3-mediated cleavage of GSDME, leading to cancer cell pyroptosis and inhibiting primary breast cancer and distant metastasis (142). Co-assembled carrier-free chemo-photodynamic nanoplatforms (A-C/NPs) of cytarabine (Ara-C) and chlorine e6 (Ce6) can induce tumor cell pyroptosis and enhance the body's immune response to breast cancer. Their specific mechanisms are the following: A-C/NPs trigger GSDME-mediated pyroptosis in a controlled manner via ROS accumulation, and Ara-C stimulates the maturation of cytotoxic T-lymphocytes, synergizing with Ce6-mediated immunogenic cell death to jointly enhance the anticancer effects of A-C/NPs. In a previous study using a mouse model of breast cancer, A-C/NPs were found to markedly inhibit *in situ*, metastatic and recurrent tumor growth (143). Current research on cellular focalization-related drugs focuses on GSDME cleavage and the regulation of the caspase-1/caspase-3 pathway. Relevant experiments have demonstrated the effectiveness of this approach for breast cancer (74,109,112). However, further studies are warranted to investigate potential adverse effects on the organism and to establish clinical application guidelines, including dosing information. Therefore, advancing the use of pyroptosis-related drugs in breast cancer should prioritize research on potential drawbacks associated with GSDME cleavage and caspase-1/caspase-3 pathway regulation.

5. Other forms of cell death and breast cancer

Current academic research on RCD in breast cancer extends beyond previously mentioned modes to include immunogenic cell death, autophagic cell death and others, all of which can both promote and inhibit the growth and metastasis of breast cancer cells. As regards immunogenic cell death, researchers have found that *Trametes robiniophila* Murr. (Huaier) increases the release of ATP and HMGB1 by promoting cell surface calreticulin exposure. Its therapeutic effects are linked to endoplasmic reticulum stress through the cAMP/PKR/eIF2α axis, both of which trigger immunogenic cell death in TNBC cells (144). Breast cancer cells produce angiopoietin-like 7 (Angptl7), a tumor-specific factor localized in the perineal regions, which contributes to the formation of necrotic apoptosis and the metastatic dissemination of the tumor core. Functional studies have shown that Angptl7 deficiency allows central necrosis and autophagy, ultimately protecting the growth of breast cancer cells and promoting their metastasis. Mechanistically, Angptl7 promotes vascular permeability and supports perineal positioning vascular remodeling (145). Current research suggests that autophagy can serve as a form of nutritional support for cellular self-repair. However, it may also contribute to tumor dormancy in breast cancer, potentially promoting chemoresistance and relapse (146,147).

6. Co-modulation of conventional chemotherapeutic agents by multiple types of RCD

Role of DOX in various types of RCD in breast cancer. In the present review, the summary of RCD in breast cancer reveals that DOX, a classic antitumor drug, interacts with various cell death pathways. In ferroptosis, DOX downregulates GPX4 and triggers excessive lipid peroxidation through the DOX-Fe^{2+} complex in the mitochondria, ultimately leading to ferroptosis-mediated cell death. Of note, the combination of ferrostatin-1 and zVAD-FMK effectively regulates ferroptosis and prevents DOX-induced cardiomyocyte death, offering potential therapeutic avenues (148). For pyroptosis, DOX accumulation leads to a cascade of events, beginning with ROS generation. ROS then stimulate the phosphorylation of JNK (specifically p-JNK), which in turn activates caspase-3, a key pyroptosis executioner. Additionally, DOX-induced ROS production also affects the cleavage of caspase-8, further promoting caspase-3 activation. Ultimately, activated caspase-3 cleaves GSDME, triggering the characteristic membrane rupture and pyroptotic cell death in breast cancer cells (132). Furthermore, DOX exhibits a direct interaction with the pyroptosis-associated protein, GSDMD, mitigating the cardiotoxic effects associated with the drug, a finding with potential clinical implications (149,150). Based on these underlying mechanisms, novel technologies have been employed to develop targeted breast cancer drugs that focus on RCD. Several promising therapeutic modalities have emerged.

As previously demonstrated, DOX-loaded hedgehog pathway inhibitor ellagic acid (EA) was combined with Cu^{2+} to develop nanoscale metal-organic frameworks (EA-Cu) modified by targeted chondroitin sulfate (151). This approach was shown to achieve the inhibition of stemness maintenance by inhibiting the hedgehog pathway through EA, while Cu^{2+} disrupted mitochondrial metabolism. This combination reduces the stemness characteristics of tumor cells and enhanced the effectiveness of DOX-mediated chemotherapy. The co-action of EA and Cu induces cuproptosis, thereby enhancing anticancer effects and preventing the development of DOX resistance (151). In summary, CS/NPs demonstrate notable antitumor effects by inducing cuproptosis and significantly inhibiting cancer cell stemness, suggesting their potential to overcome resistance to cancer chemotherapy (151).

Emerging therapeutic modalities targeting ferroptosis utilize this interaction. One such modality utilizes degraded bimetallic nanoparticles-7% Fe-doped ZIF-8 encapsulated with DOX, a classical drug used in the treatment of breast cancer. This approach inhibits the growth and metastasis of breast cancer cells by utilizing ferroptosis to induce the production of ROS in cancer cells (152). Several studies have explored strategies with which to mitigate the side-effects of DOX, while harnessing its antitumor effects. For example, isoliquiritin, a natural compound, inhibits the NF-κB signaling pathway, which regulates ferroptosis in breast cancer and improves resistance to DOX (153). Additionally, decreasing the levels of GSDME protein, a key factor in pyroptosis, can minimize DOX-induced cardiotoxicity and pyroptosis in breast cancer cells (132).

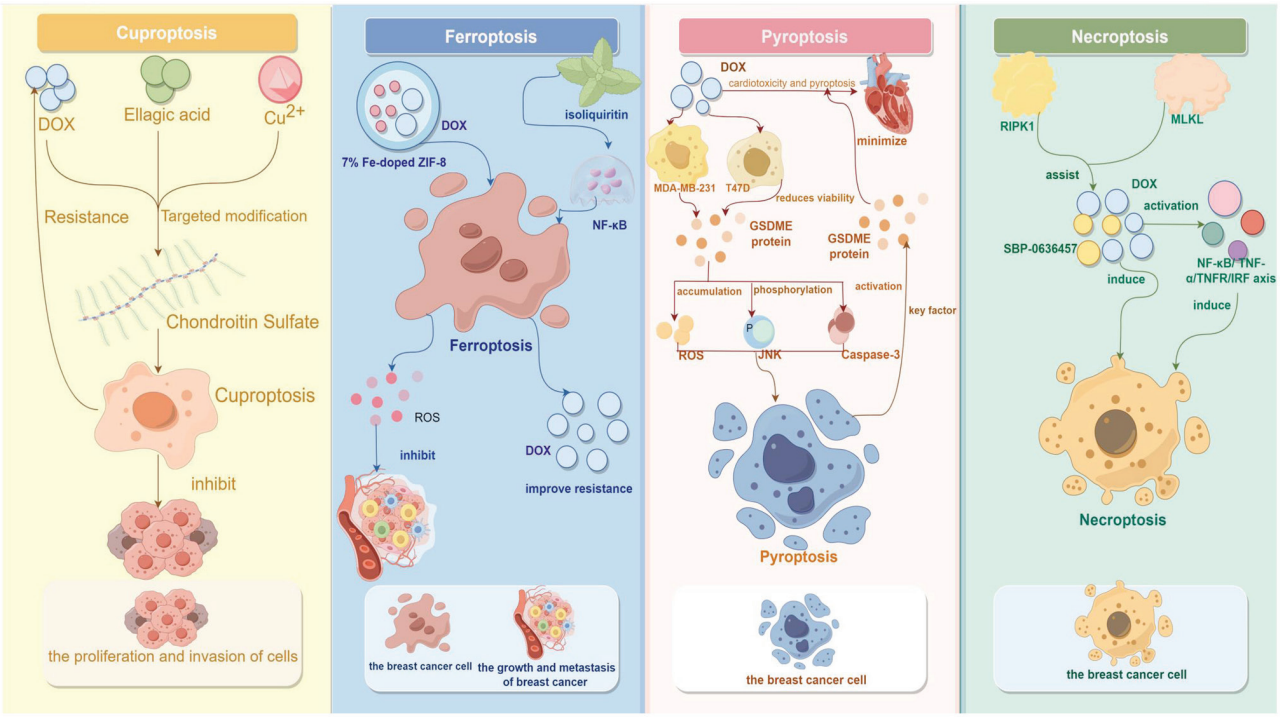

Figure 1. Comparison of the bidirectional effects of doxorubicin in relation to multiple types of regulated cell death. DOX, doxorubicin; ROS, reactive oxygen species. The figure was prepared using Figdraw.

While DOX itself can induce necroptosis, activating the NF-κB/TNF-α/TNFR/IRF axis further enhances this process, resulting in the SBP-0636457/DOX-induced necrosis of breast cancer cells (154) (Fig. 1).

Adjuvant drugs can also be utilized to modulate the anticancer effects of DOX through the regulation of RCD. It has been shown that plant extracts containing magnoflorine (Mag) significantly enhance the effects of DOX on the induction of autophagy by increasing the expression of light chain 3 (LC3)-II. Notably, combined treatment with DOX and Mag significantly inhibits the activation of PI3K/AKT/mTOR signaling pathway (155). Conversely, it promotes the p38 MAPK pathway, leading to the induction of both autophagy and apoptosis. These findings suggest that Mag may potentiate the anticancer effects of DOX and enhance the sensitivity of breast cancer cells to this chemotherapeutic agent (155). As a cornerstone of breast cancer chemotherapy, the diverse roles of DOX in regulating cell death remain under active investigation. Future research within the academic community is expected to uncover additional functions of doxorubicin and targeted drugs in this context.

RCD and cisplatin. In addition to DOX, cisplatin also exhibits diverse interactions with RCD pathways in breast cancer. As a potent metallochemotherapeutic agent, cisplatin can overcome resistance through various mechanisms. One approach involves the induction of cuproptosis by constructing copper(II) bis(diethyldithiocarbamate) (CuET). This increases CuET distribution in the cytoplasm and cytoskeleton, effectively bypassing cisplatin resistance (156). Furthermore, cisplatin has been shown to induce ferroptosis, another form of RCD, to overcome resistance (157). The overexpression of the ferroptosis driver, SOCS1, inhibits proliferation and promotes ferroptosis in TNBC cells, modulating cisplatin resistance (158). Additionally, inhibiting the ferroptosis-related gene, GPX4, which eliminates ROS crucial for ferroptosis, sensitizes tumor cells to cisplatin. Research using nude mouse models has demonstrated that combining cisplatin with the GPX4 inhibitor, RSL3, significantly reduces tumor growth compared to either treatment alone (159). These findings suggest that GPX4 inhibition suppresses ferroptosis and enhances the anticancer effects of cisplatin. Cisplatin can also promote pyroptosis, another RCD pathway. By upregulating MEG3, it activates the NLRP3 inflammasome, leading to caspase-1-dependent pyroptosis. This activation cleaves GSDMD, releasing fragments that form membrane pores. Moreover, caspase-1 promotes the maturation and secretion of IL-18 and IL-1β, ultimately inducing the focal death of breast cancer cells and exerting antitumor effects (160) (Fig. 2). Notably, cisplatin can also induce autophagy, a cellular self-degradation process. It upregulates several autophagy-related genes, including *AMBRA1, ATG3, ATG4C, ATG4D, ATG5, ATG7, ATG13, ATG14, ATG16L2, Beclin1, DRAM1, GABARAP, GABARAPL1, GABARAPL2, HDAC6, IRGM, MAP1LC3B* and *ULK1 in*volved in the induction, vesicle nucleation and elongation phases of autophagy, suggesting that it inhibits cell proliferation and growth in breast cancer through multiple RCD mechanisms (161). Overall, these findings suggest that inducing various forms of RCD can effectively reduce cisplatin resistance and enhance its anticancer effects in breast cancer.

7. Comparison and co-action of multiple types of RCD

Specific features of RCD. RCD stands apart from accidental cell death, which results from uncontrolled damage exceeding

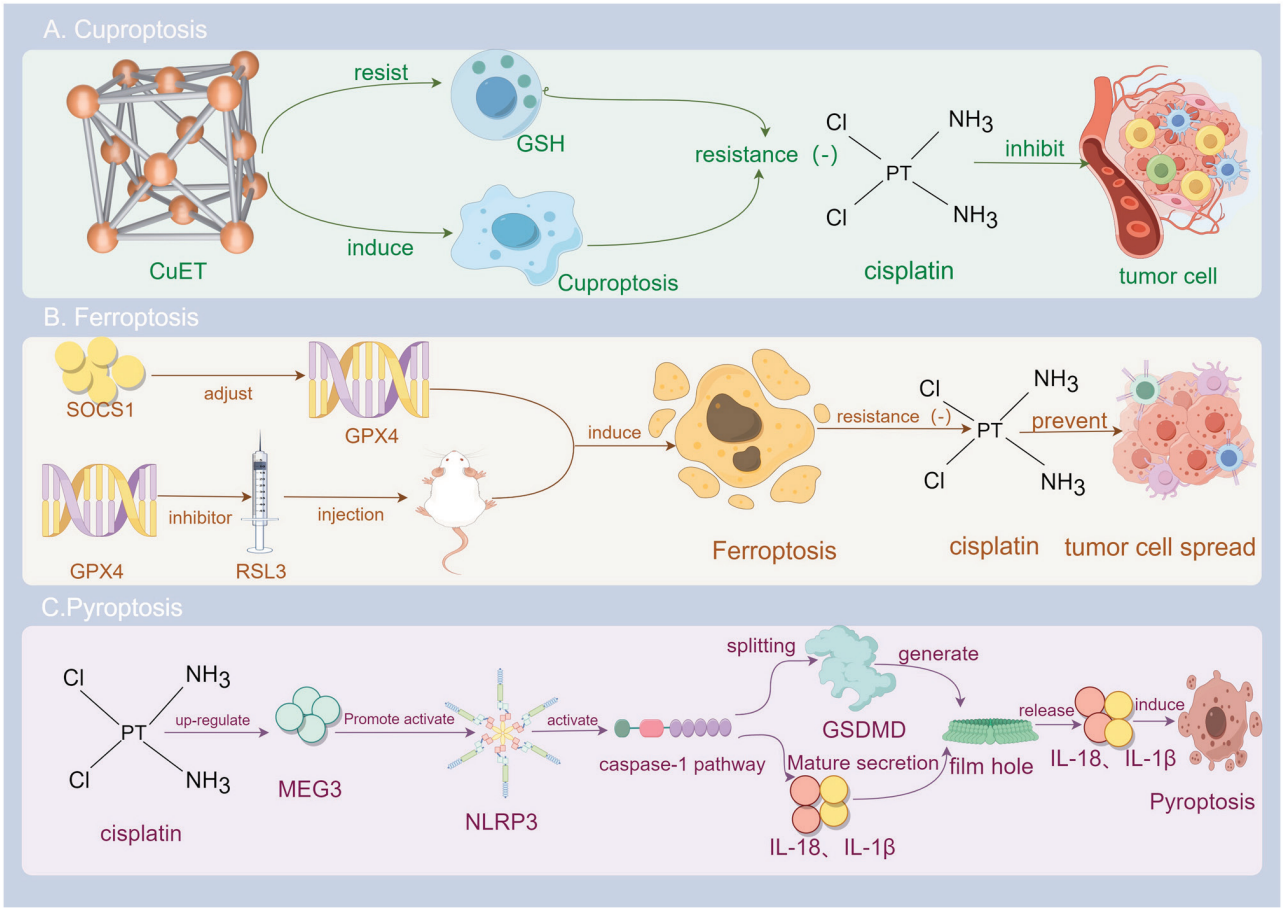

Figure 2. Comparison of different types of regulated cell death modulating the conventional chemotherapeutic agent, cisplatin. GPX4, glutathione peroxidase 4; GSH, glutathione; GSDMD, gasdermin D. The figure was prepared using Figdraw.

the survival threshold of a cell. Unlike its chaotic counterpart, RCD is a genetically controlled and orderly process that maintains internal stability (162). The present review showcases the ability of RCD to selectively target tumor cells, hindering their growth and spread. As such, RCD emerges as a promising avenue for cancer therapy.

Comparison of different types of mechanisms for RCD. Various forms of RCD exist, each with unique regulatory mechanisms. Cuproptosis is triggered by the direct interaction of copper with thiooctylated components of the TCA cycle. This interaction leads to the aggregation of these proteins and the depletion of iron-sulfur cluster proteins, inducing proteotoxic stress and, ultimately, cell death (16). By contrast, ferroptosis is characterized by iron-dependent lipid peroxidation damage within the mitochondria, primarily caused by the reduced activity of the GPX4 enzyme (163). Pyroptosis, on the other hand, is activated by external stimuli that induce the formation of inflammatory vesicles. These vesicles activate caspase-1, which disrupts the cell membrane and leads to the release of IL-1β and IL-18 cytokines. The combined action of these cytokines then induces pyroptosis in the affected cell (164) (Fig. 3). Although the detailed mechanisms of each RCD type differ, they all share the characteristic of being initiated by the intrinsic regulatory processes of the cell. Cells that have not initiated these processes remain alive. This understanding highlights the potential of RCD as a novel approach to cancer therapy. Research in this area has already shown promise in improving the accuracy of treatment and patient outcomes.

Oxidative stress: A common mode of causing multiple types of RCD. Oxidative stress, characterized by the accumulation of ROS, plays a critical role in triggering various forms of RCD in cancer cells. Recent studies have shed light on the crucial role of *MTF1*, a gene associated with cuproptosis. Notably, its expression differs in tumor cells compared to normal cells, and reducing MTF1 levels can elevate ROS production and initiate cuproptosis (165). Similarly, the buildup of ROS is crucial for ferroptosis, another form of RCD. Polyunsaturated fatty acids, a hallmark of ferroptosis, are produced when ROS attack the double bonds in lipids (166). For pyroptosis, ROS trigger the activation of the NLRP3 inflammasome, which initiates and activates NLRP3 synthesis. This inflammasome acts as the key player in initiating pyroptosis (167). In summary, oxidative stress plays a pivotal role in triggering various forms of RCD in cancer cells. This understanding opens new avenues for developing synergistic cancer therapies that leverage multiple RCD modalities.

RCD and conventional chemotherapeutic agents. As aforementioned, the induction of cuproptosis, ferroptosis and pyroptosis can enhance the anticancer properties of drugs,

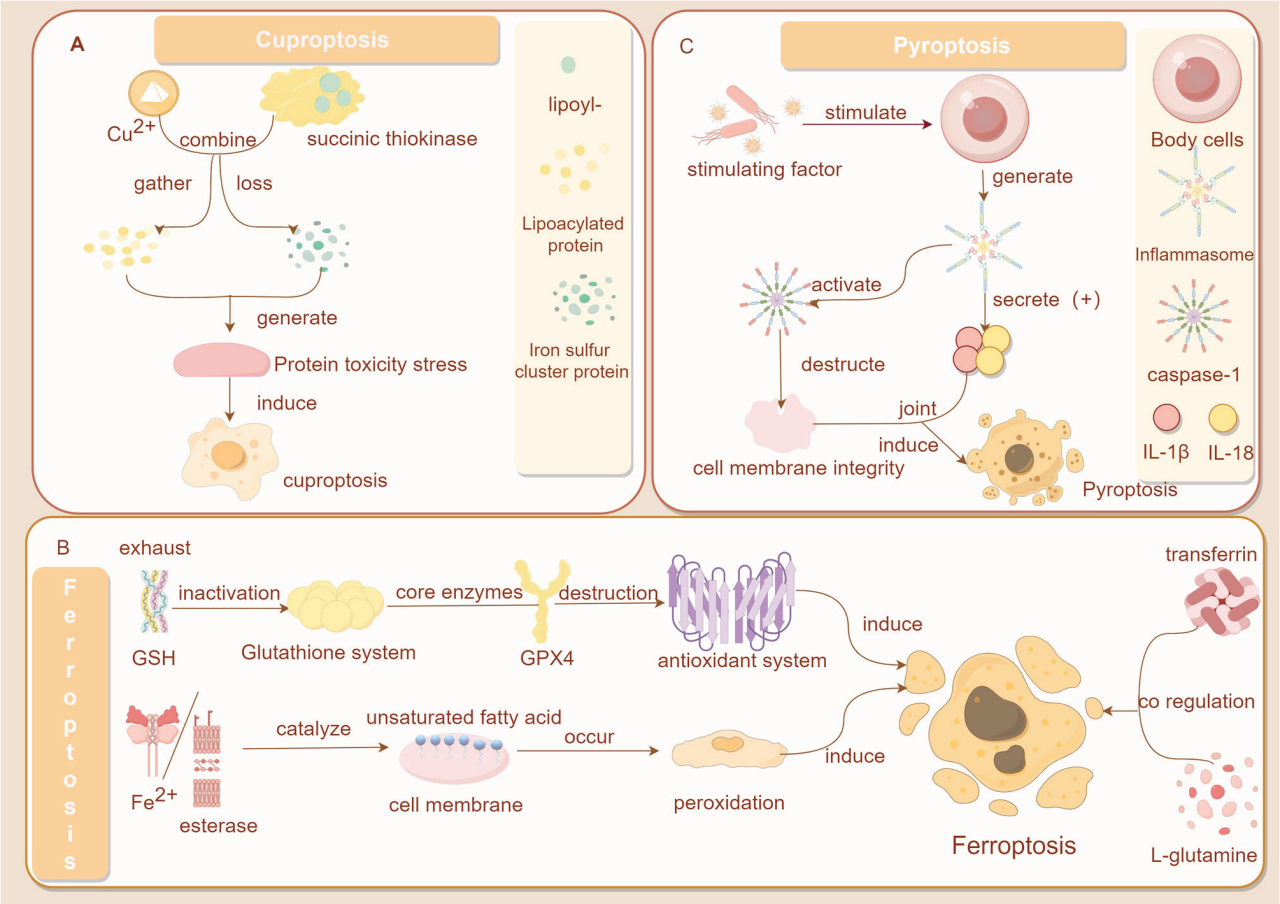

Figure 3. Comparison of the mechanisms of cuproptosis, ferroptosis and cellular pyroptosis. GSH, glutathione; GPX4, glutathione peroxidase 4. The figure was prepared using Figdraw.

such as DOX and cisplatin, while reducing their resistance and side-effects. This research also suggests the potential to develop predictive models based on lncRNAs associated with cuproptosis. These models could help determine the sensitivity of patient with breast cancer to various chemotherapeutic agents (such as lapatinib, phenelzine, vincristine and etanercept), aiding in the selection of personalized treatment regimens (168). Furthermore, the protein, RelB, provides evidence for the influence of ferroptosis on chemotherapeutic response. RelB promotes resistance to tamoxifen by upregulating GPX4, an enzyme that inhibits ferroptosis (169). Similarly, miR-155-5p supports the role of pyroptosis in response to therapy. *In vivo* research has demonstrated that decreasing miR-155-5p levels triggers pyroptosis and enhances the effectiveness of the drug, cetuximab, against TNBC cells (170). These findings suggest that RCD research can not only lead to the discovery of new drugs, but may also shed light on the anticancer potential and resistance mechanisms of existing drugs.

Interactions of forms of RCD. There is a potential association between various RCD modes. Cuproptosis and ferroptosis regulators exhibit the same mutation frequency in breast cancer. As previously demonstrated, the knockdown of the ferroptosis regulator, ATF2, in breast cancer cells (MCF7) resulted in marked changes in cuproptosis regulators (DLST, GCSH, PDHA1, LIPT1 and DLD) (171). Furthermore, the unsupervised clustering of cuproptosis and ferroptosis regulators identified three distinct copper/ferroptosis regulator clusters named CuFecluster A, B and C. These three regulator clusters have different biological functions. The three regulatory factor clusters have distinct biological functions, which strengthen the experimental basis for using RCD for tumor therapy. CuFecluster B is associated with the full activation of immunity, including the B-cell receptor signaling pathway, natural killer cell-mediated cytotoxicity, antigen processing and presentation, cytokine-cytokine receptor interactions and chemokine signaling pathway. Additionally, CuFecluster B is enriched in various activated immune cells and is classified as an immunoinflammatory phenotype. CuFecluster A is associated with various cellular proliferative processes, particularly mismatch repair, DNA replication and the cell cycle. Notably, CuFecluster A is more strongly associated with innate immune cells (including myeloid-derived suppressor cells, eosinophils, natural killer cells, monocytes, mast cells and macrophages). Finally, CuFecluster C exhibits a limited association with immune cells and suppresses immune responses, consistent with the main features of the immune desert phenotype (171). Different clusters of regulatory factors can be harnessed, therefore, to open new avenues for future breast cancer therapy. In conclusion, while this study has summarized the interactions and derived functions of cuproptosis and ferroptosis in breast

Table I. Utilization of scientifically and technologically constructed drugs related to regulated cell death.

Drug	Target of action/mechanism	Regulatory cell death involved	Potency	(Refs.)
Type-I AIE photosensitizer loaded biomimetic system	Lipoylated protein aggregation and iron-sulfur protein loss	Cuproptosis	Inhibits lung metastasis of breast cancer and prevents tumor rechallenge	(61)
HD/BER/GOx/Cu hydrogel system	Produces starvation/ chemodynamic therapy and induces copper death	Cuproptosis	Preoperative reduction of breast cancer size to facilitate surgical excision	(62)
Heparanase-driven sequential released nanoparticles	Effectively enhances intracellular ROS levels and activates the iron death pathway. Enhanced ROS also induces the apoptotic pathway and reduces the expression of MMP-9	Ferroptosis	New dosage regimens for the treatment of breast cancer by intracellular and extracellular mechanisms	(93)
Polydopamine nanoparticles	Combination with DOX induces ferroptosis in breast cancer cells	Ferroptosis	Possesses anti-tumor activity and selectivity, increasing the accuracy and effectiveness of targeted therapies	(94)
Cinnamaldehyde dimers	Depletion of glutathione, in combination with the anti-breast cancer drug sorafenib (sorafenib.SRF), resulted in a significant enhancement of iron death, and by promoting dendritic cell maturation and $CD8^+$ T-cell initiation	Ferroptosis	Increasing the anticancer effects of sorafenib	(95)
erastin@FA-exo	Inhibits the expression of GPX4 and upregulates the expression of CDO1	Ferroptosis	May reduce side effects in tumor therapy and may replace traditional erastin in clinical practice	(96)
Biomimetic nanoparticle (BNP) loaded with indocyanine green (ICG) and decitabine (DCT)	Induced cleavage of GSDME	Pyroptosis	Controlled tumor growth and stimulated anticancer immune responses	(139)
Carrier-free chemo-photodynamic nanoplatform	Triggering GSDME-Mediated ScorchDeath in a controlled manner via ROS accumulation	Pyroptosis	Complement chemotherapy or immunotherapy for cancer metastasis	(140)

HD, hyaluronic acid-dopamine; BER, berberine hydrochloride; GOx, glucose oxidase; ROS, reactive oxygen species; DOX, doxorubicin; GSDME, gasdermin E.

cancer, associations with other RCDs are still under investigation. Nevertheless, this work provides valuable insights for exploring the relationships between other regulatory death pathways in the future, potentially leading to new benefits for breast cancer patients.

Summarizing the role of various forms of RCD in tumor cells in breast cancer reveals that various RCD pathways can inhibit cancer cell proliferation and invasion. Additionally, they can reduce resistance to conventional chemotherapeutic drugs. Combining multiple RCD modalities in breast cancer therapy holds promise for synergistic effects and offers a promising new avenue for treatment.

8. Importance of multiple types of RCD for breast cancer

Importance of cuproptosis for breast cancer cells. It has been established that cuproptosis-associated genes can predict the prognosis of patients with breast cancer and provide information about the immune microenvironment. Cox regression analyses identified high expression of the cuproptosis-associated gene, SLC31A1, as an independent prognostic factor for a shorter overall survival. Additionally, a high SLC31A1 expression has been shown to be associated with dysregulated immune responses; specifically, it has been shown to be negatively associated with the level of infiltration of CD8 T-cells

and activated natural killer cells (53). Furthermore, targeting cuproptosis with existing drugs may provide new avenues for the treatment of breast cancer. Zinc pyrithione (ZnPT), typically used for fungal treatment, promotes the aggregation of *DLAT* both *in vitro* and *in vivo*. *DLAT* is a biomarker of cuproptosis and ZnPT disrupts copper homeostasis, eventually leading to cuproptosis in TNBC cells. This, in turn, inhibits their viability and proliferation (172). Overall, cuproptosis plays a crucial role in predicting and treating breast cancer, holding significant value for exploring genetic detection methods and repurposing existing drugs for anticancer effects.

Importance of ferroptosis for breast cancer cells. In ferroptosis, the activation status is of the pathway is significantly associated with clinical outcomes and intra-tumor heterogeneity in breast cancer. The detection of NDUFA13 expression levels provides a means with which to infer this activation status (173). Notably, ferroptosis-related genes extend beyond predicting patient prognosis, also playing an immunologically active role in immunotherapy.

For example, compared with normal samples, tumor samples exhibit a significantly lower expression of the ferroptosis-related gene, *HIC1*. Notably, *HIC1* expression varies across different clinical stages of breast cancer. Furthermore, *HIC1* significantly participates in immune-related biological functions and signaling pathways, with its expression being directly associated with the response to PD-1/PD-L1 inhibitors in cancer therapy (174). Beyond enhancing the chemotherapeutic efficacy (as aforementioned), ferroptosis can also potentiate radiotherapy in breast cancer. Constructing tumor microenvironment-degradable nanohybrids that incorporate ferroptosis in a dual radiosensitization mode markedly improves therapeutic efficacy and anti-metastatic efficiency (175). Overall, ferroptosis is significantly associated with early breast cancer invasion and recurrence, highlighting its importance in treatment comprehensiveness and predictive accuracy. Not only are ferroptosis-related genes used for patient prognosis, but also channel proteins are being explored to further enhance prediction accuracy. Consequently, ferroptosis provides a multifaceted approach for the treatment of breast cancer, capable of augmenting the efficacy of both chemotherapy and radiotherapy.

Importance of pyroptosis for breast cancer cells. In cellular pyroptosis, certain lncRNAs associated with the pathway can predict the prognosis of patients with breast cancer. For instance, a higher expression of RP11-459E5.1 has been shown to be associated with a poorer overall survival, while high levels of RP11-1070N10.3 and RP11-817J15.3 are associated with an improved survival (176). Additionally, pyroptosis-related genes can even predict the potential target organs for breast cancer metastasis. The analysis of patients with TNBC and brain metastases has revealed significant differences in AIM2 and ZBP1 expression between primary tumors and metastases. Notably, a high AIM2 expression predictsa worse prognosis, while a high ZBP1 expression suggests improved outcomes, suggesting their potential as biomarkers for TNBC brain metastasis (177). Furthermore, chemotherapeutic agents capable of inducing pyroptosis have promising potential for use in the treatment of breast cancer. Derivatives, such as 3-acyl isoquinoline-1 (2H)-ones can trigger GSDME-mediated pyroptosis, leading to apoptosis and inhibiting the proliferation of breast cancer cells without harming normal breast cells (178). The unique advantage of pyroptosis lies in the ability of related genes to predict metastatic organs and the relative lack of toxicity of its associated drugs towards normal cells, both contributing to improved patient prognosis.

Across cuproptosis, ferroptosis and pyroptosis, various molecules can be used to predict the prognosis of patients with breast cancer. Additionally, targeting these pathways or their mechanisms through drug development presents opportunities to enhance treatment efficacy. All three types of RCD hold immense potential for future research and breast cancer treatment. While ferroptosis research currently boasts more applied and comprehensive studies, including prognostic prediction encompassing developmental stages, it is important to acknowledge the ongoing investigation and promise of cuproptosis and pyroptosis as well. Moreover, ferroptosis-related drugs may enhance not only chemotherapy, but also radiotherapy, potentially rendering it the first form of RCD to reach clinical application.

9. Conclusion and future perspectives

Breast cancer poses a significant threat to human life and health. Its growth, development and metastasis are intricately linked to the body's own gene regulation and immune defense mechanisms. RCD, an intrinsic component of these physiological programs, plays a crucial role in tumor regulation and defense. The academic community is steadily uncovering and proposing the regulatory mechanisms of cuproptosis, ferroptosis, pyroptosis and other forms of RCD in breast cancer. The development of novel drugs and ongoing clinical trials (presented in Table I) highlight the strong association between these pathways and breast cancer, offering a promising new direction for research. Several emerging drugs and clinical agents have demonstrated the ability to induce RCD in breast cancer cells. However, ongoing research is necessary to fully understand the potential mechanisms of RCD and further explore and test related drugs in clinical trials. By harnessing the power of RCD, it is hoped that future advancements in treatment can improve treatment efficacy, enhance the quality of life, and increase the survival rate of patients with breast cancer.

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Availability of data and materials

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Authors' contributions

LA, CQ, WH, KZ, QH, LJ and HL searched the literature for related studies for the review and prepared the manuscript and figures. LL and NY provided constructive guidance and made critical revisions. LA participated in the main editing of the manuscript. LA, CQ, LL and NY participated in the design of the review. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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