Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 10
MMTCS 2026

Emerging Forms of Regulated Cell Death Modalities Associated with Immunogenic Cell Death and Their Translational Potential in Cancer Immunotherapy

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Abstract. Tumor immunotherapy has demonstrated significant clinical value in various malignancies by activating the host antitumor immune response. However, its clinical benefits are still limited by factors such as insufficient tumor immunogenicity, an immunosuppressive tumor microenvironment (TME), and acquired drug resistance. Inducing immunogenic cell death (ICD) in tumor cells can promote the release of tumor antigens, the exposure of danger signals, and antigen presentation, thereby facilitating the conversion of certain “cold” tumors into “hot” tumors and enhancing the response to immunotherapy. In recent years, the relationship between regulated cell death (RCD) and ICD has received widespread attention. Nevertheless, not all forms of RCD possess equivalent immunogenicity; different RCD modalities exhibit varying degrees of potential to induce ICD, remodel the tumor immune microenvironment, and synergize with immune checkpoint inhibitor (ICI) therapy. This review focuses on several RCD types that have been actively researched in recent years and show clear associations with ICD—including ferroptosis, pyroptosis, necroptosis, cuproptosis, and disulfidptosis—summarizing their mechanistic links to ICD, their roles in immune regulation, and their translational prospects in tumor immunotherapy. It further discusses the current challenges in the field and future research directions.

Keywords: Tumor immunotherapy; Immunogenic cell death; Regulated cell death; Ferroptosis; Pyroptosis; Necroptosis; Cuproptosis; Disulfidptosis; Immune checkpoint inhibitors; Tumor microenvironment.

1. Introduction

Tumor immunotherapy represents a major direction in current cancer treatment. In particular, immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 and CTLA-4 have achieved remarkable efficacy in multiple solid tumors [1]. However, the clinical benefits of ICIs are still constrained by factors such as primary non-response, acquired resistance, immune-related adverse events, and insufficient predictive power of biomarkers [2-3]. This is particularly evident in immunologically “cold” tumors with low immunogenicity, such as microsatellite-stable colorectal cancer, pancreatic cancer, and prostate cancer, where ICIs often fail to elicit robust antitumor immune responses, resulting in limited therapeutic efficacy [4-6]. Therefore, strategies aimed at enhancing tumor cell immunogenicity and reprogramming the immunosuppressive TME to initiate effective antitumor immunity have become a central focus of current tumor immunotherapy research.

In this context, the concept of immunogenic cell death (ICD) provides a novel theoretical foundation for improving responses to tumor immunotherapy [7]. ICD is characterized not only by tumor cell death but also by the release of tumor antigens and the exposure or secretion of damage-associated molecular patterns (DAMPs). For example, calreticulin (CRT) can be exposed on the surface of tumor cells. Meanwhile, high mobility group box 1 (HMGB1), adenosine triphosphate (ATP), and heat shock proteins (HSPs) can be released into the extracellular space [8]. These signals facilitate the recruitment and maturation of dendritic cells and their uptake of tumor antigen, thereby enhancing antigen presentation and $CD8^+$ T cell-mediated adaptive antitumor immunity. Consequently, ICD

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serves as a critical bridge linking tumor cell death, immune microenvironment remodeling, and immunotherapy sensitization [9].

In recent years, the spectrum of regulated cell death (RCD) has continued to expand [10], offering new entry points for inducing ICD and enhancing tumor immunotherapy. Various RCD modalities can participate in DAMP release, antigen exposure, inflammatory signal activation, and tumor immune microenvironment remodeling through distinct molecular mechanisms, exhibiting varying degrees of crosstalk with ICD. However, not all RCD modalities are inherently immunogenic or qualify as ICD; different forms of cell death differ in the strength of immunogenicity, induction conditions, degree of inflammatory response, and in vivo controllability [11]. Accordingly, this review focuses on RCD types that have been actively investigated in recent years and demonstrate relatively clear associations with ICD—including ferroptosis, pyroptosis, necroptosis, cuproptosis, and disulfidptosis [12]—and summarizes their mechanistic connections with ICD as well as their potential value in sensitizing tumors to immunotherapy.

2. Basic Mechanisms and Molecular Features of ICD

2.1. Core Characteristics of ICD

Immunogenic cell death (ICD) is not merely a regulated form or modality of cell death, but a form of death that simultaneously provides antigenicity and adjuvanticity. Its core feature lies in the fact that dying tumor cells not only release tumor-associated antigens but also trigger the exposure or secretion of a series of damage-associated molecular patterns (DAMPs), enabling effective recognition by the immune system. Many classical ICD inducers, such as anthracycline chemotherapeutic agents, oxaliplatin, radiotherapy, and photodynamic therapy, commonly promote the spatiotemporally ordered release or exposure of DAMPs through pathways including endoplasmic reticulum (ER) stress, reactive oxygen species (ROS) generation, and the unfolded protein response (UPR). It is widely recognized that ER stress, ROS production, calreticulin (CRT) exposure, ATP secretion, and HMGB1 release represent critical molecular events in the classical ICD process [12-13].

2.2. Major Molecular Markers of ICD

The key molecular markers of ICD primarily include CRT, ATP, and HMGB1. In addition, Annexin A1 (ANXA1), heat shock proteins, type I interferons, and chemokines also contribute to enhancing its adjuvant immune effects.

Calreticulin (CRT): During the early phase of cell death, CRT translocates from the ER lumen to the cell surface, serving as an “eat me” signal. It binds to the CD91 receptor on dendritic cells (DCs), thereby promoting the phagocytosis of dying tumor cells and subsequent antigen presentation [13].

Extracellular ATP: Released into the extracellular space through autophagy-dependent secretion and other mechanisms, extracellular ATP acts as a “find me” signal that promotes the recruitment of antigen-presenting cells. It also participates in inflammasome activation and the regulation of immune cell functions via purinergic receptors [12].

High Mobility Group Box 1 (HMGB1): Typically released from the nucleus during the late phase of cell death, HMGB1 binds to pattern recognition receptors on antigen-presenting cells such as DCs, thereby promoting DC maturation and antigen presentation [14].

Furthermore, surface exposure of heat shock proteins (HSP70/HSP90), release of Annexin A1 (ANXA1), secretion of type I interferons (IFN-I), and CXCL10 also contribute to enhancing the adjuvant effects. The orderly appearance of these DAMPs—CRT in the early phase, ATP in the intermediate phase, and HMGB1 in the late phase—enables dying tumor cells to transition from passive targets of clearance to active sources of signals that stimulate antitumor immune responses[13].

2.3. ICD-Mediated Antitumor Immune Activation

ICD can convert "danger signals" into "activation signals" that initiate adaptive immunity, driving dendritic cells (DCs) maturation and antigen cross-presentation, thereby eliciting tumor-specific T cell responses [15-16]. Meanwhile, ICD may indirectly attenuate immunosuppressive cellular components in the TME—such as myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and M2-type tumor-associated macrophages (M2 TAMs)—by altering the profiles of cytokines, chemokines, and antigen presentation status, ultimately reprogramming the immunosuppressive TME [17-18].

Once activated, cytotoxic T lymphocytes (CTLs) home to the tumor site and directly kill viable tumor cells by releasing interferon-gamma (IFN-γ) and granzymes [19]. Moreover, IFN-γ can promote tumor cell ferroptosis, while granzyme-mediated cleavage of gasdermin family proteins may trigger pyroptosis-like inflammatory cell death in certain contexts. These secondary immunogenic or inflammatory cell death processes may further amplify DAMP release, antigen presentation, and T cell responses, thereby forming a positive feedback loop of immune activation [20-22].

3. Emerging Regulated Cell Death (RCD) Types Associated with ICD and Their Mechanisms

Compared with non-lytic apoptosis, necroptosis may elicit stronger ICD-like immune activation under appropriate conditions because of its lytic membrane rupture and substantial DAMP release. Based on the above criteria, this section discusses five non-apoptotic RCD modalities—ferroptosis, pyroptosis, necroptosis, cuproptosis, and disulfidptosis—that have been linked to ICD-like immunogenicity in cancer. These modalities are organized according to their death mechanisms, ICD-related evidence, effects on the tumor immune microenvironment, and combination therapy potential. [23-24].

3.1. Ferroptosis and ICD

Ferroptosis is an iron-dependent form of RCD driven by lipid peroxidation, characterized by the accumulation of polyunsaturated fatty acid-containing phospholipid hydroperoxides that ultimately lead to membrane damage [25]. Morphologically, ferroptotic cells exhibit mitochondrial shrinkage, increased membrane density, and reduced or absent cristae. Its core regulatory network involves iron metabolism, lipid metabolism, the system Xc^--GSH-GPX4 axis, the FSP1-CoQ10 axis, and TP53-related signaling pathways. Unlike apoptosis and pyroptosis, ferroptosis does not rely on classical caspase pathways but is primarily regulated by the interplay of iron homeostasis, redox balance, and lipid metabolism.

Ferroptosis-associated immunogenicity is mainly attributed to iron-dependent lipid peroxidation, which causes oxidative membrane damage and, at specific stages, promotes the release of ATP, HMGB1, and oxidized lipid mediators [26]. Wiernicki et al. conducted a stage-specific analysis of the immunogenicity of ferroptotic cancer cells, noting that the intermediate stage is associated with ATP release, while the terminal stage correlates with HMGB1 release and plasma membrane rupture. In contrast, early-stage ferroptotic cells may impair dendritic cell maturation and cross-presentation in certain models [27]. These findings indicate that the immunogenicity of ferroptosis is not a fixed attribute but exhibits clear stage- and context-dependency. It must be evaluated comprehensively based on the induction method, stage of cell death, extent of lipid peroxidation, and the tumor immune microenvironment [24].

The impact of ferroptosis on the tumor immune microenvironment is bidirectional: moderate ferroptosis may enhance immunogenicity, whereas excessive lipid peroxidation or ferroptosis in immune cells may suppress antitumor immunity. On one hand, DAMPs and lipid mediators released by ferroptotic tumor cells can promote DC maturation, macrophage repolarization, and $CD8^+$ T cell infiltration, thereby converting "cold" tumors into a more immunogenic state. On the other hand, excessive lipid peroxidation products may induce chronic inflammation or immunosuppressive

signals and induce ferroptosis in $CD8^+$ T cells within the TME, thereby weakening their antitumor effects. Additionally, ferroptotic tumor cells may impair DC phagocytic function and antigen presentation efficiency under certain conditions. Therefore, ferroptosis is not inherently a purely pro-immunogenic process; its immunological outcome depends on cell type, extent of death, lipid metabolic status, and TME context.

At the immune-cell level, differences in immune cell sensitivity to ferroptosis significantly influence the immune landscape of the TME. M2-type tumor-associated macrophages (TAMs) resist ferroptosis through high GPX4 expression or optimized lipid metabolism, thereby maintaining their immunosuppressive function. In contrast, M1-type TAMs produce nitric oxide radicals ($NO\cdot$) via high inducible nitric oxide synthase expression, which neutralizes lipid radicals, rendering them relatively resistant to ferroptosis even in the absence of GPX4 [28]. Thus, inducing ferroptosis in immunosuppressive cells or promoting M2-to-M1 repolarization can reverse the immunosuppressive state of the TME. Additionally, immune effector cells regulate tumor cell sensitivity to ferroptosis through cytokine release. IFN-γ secreted by $CD8^+$ T cells activates the JAK-STAT1 pathway, downregulates System Xc^- expression, reduces cystine uptake and GSH synthesis, and ultimately triggers ferroptosis in tumor cells [20,22].

Ferroptosis inducers can enhance tumor immunogenicity by releasing HMGB1, ATP, and lipid peroxidation products, thereby promoting antigen presentation and T cell infiltration and potentiating the efficacy of immune checkpoint inhibitors. Recent studies support the therapeutic value of combining ferroptosis induction with immunotherapy. For example, Bao Y et al. [29] developed an Fc-SS-Fe/Cu nanosystem that promotes ferroptosis and lipid peroxidation (LPO) accumulation via mild photothermal therapy (PTT), inducing ICD and thereby enhancing anti-PD-L1 therapeutic efficacy. Peng H et al. [30] developed a hollow ZIF-8 metal-organic framework (MOF) coated with mesenchymal stem cell membrane (MSCm) as a biomimetic carrier. Through copper-free click chemistry, it was loaded with Paris saponin II (PPII) functionalized with triphenylphosphonium (TPP) for mitochondrial targeting. The results showed that ferroptosis enhanced CRT exposure and HMGB1 release, promoted dendritic cell (DC) maturation, repolarized TAMs from M2 to M1 phenotype, increased cytotoxic T cell infiltration, and suppressed regulatory T cells (Tregs), synergistically enhancing tumor immunogenicity when combined with anti-PD-L1 therapy. These findings suggest that ferroptosis induction can serve as an important sensitization mechanism for immune checkpoint blockade (ICB).

3.2. Pyroptosis and ICD

Pyroptosis is a highly inflammatory form of regulated cell death primarily driven by inflammasome activation, caspase-1 signaling, and cleavage of gasdermin family proteins. In the canonical pathway, inflammasome activation leads to caspase-1 activation, which cleaves GSDMD to release its N-terminal domain. This forms pores in the cell membrane, resulting in cell swelling, loss of membrane integrity, and leakage of cellular contents. In non-canonical pathways, caspase-4/5/11, caspase-3, or granzymes can cleave different gasdermin members and induce similar membrane pore formation.

Pyroptosis can exhibit prominent ICD-like immunogenic features under appropriate conditions. Its immunogenicity primarily arises from gasdermin-mediated membrane pore formation and cell lysis. During pyroptosis, gasdermin-mediated membrane pores promote the rapid release of DAMPs, including ATP, HMGB1, and mitochondrial DNA (mtDNA), while inflammasome-activated caspase-1 processes pro-IL-1β and pro-IL-18 into their mature forms, which are subsequently released into the extracellular space. This sequential process of "membrane pore formation–cell lysis–inflammatory factor maturation and release" enables pyroptotic cells to simultaneously provide danger signals, inflammatory stimuli, and tumor antigen sources, thereby creating a typical immunogenic death microenvironment [31-32].

In the tumor immune microenvironment, pyroptosis can activate both innate and adaptive immune responses through the rapid release of DAMPs and mature IL-1β/IL-18. These cytokines strongly

activate multiple immune subsets within the TME, including natural killer (NK) cells and T cells [33]. IL-1β promotes DC maturation and antigen presentation via IL-1R1-dependent NF-κB activation [34]. Meanwhile, IL-18 enhances the cytotoxic activity of NK cells and T cells and increases the production of effector molecules such as perforin, granzymes, and IFN-γ [33]. Furthermore, granzymes released by CTLs or NK cells can cleave GSDMB, inducing secondary pyroptosis in tumor cells and forming a positive feedback loop between immune killing and cell death, which further amplifies antitumor immunity and improves tumor control [35].

Consequently, pyroptosis promotes the infiltration of effector T cells, NK cells, and pro-inflammatory myeloid cells, converting the immunosuppressive "cold" tumor microenvironment into an immune-activated "hot" state. Wang Q, et al. [36] used a nanoparticle delivery system to deliver the mouse GSDMA homolog Gsdma3 and induce tumor cell pyroptosis, which enhanced antitumor immunity by increasing effector immune-cell infiltration, reducing immunosuppressive cells, and upregulating immune-activation programs. Xi G et al.[37] further reported that GSDMD expression positively correlates with $CD8^+$Tcell effector gene signatures in pan-cancer analysis, suggesting a potential association between gasdermin-mediated pyroptosis and cytotoxic immune activity.

3.3. Necroptosis and ICD

Necroptosis is a lytic form of regulated cell death (RCD) orchestrated by the RIPK1–RIPK3–MLKL axis. It is characterized by the loss of plasma membrane integrity and the subsequent release of cellular contents. This process is typically triggered by death receptors, pattern recognition receptors, or viral sensing signals. When caspase-8 is inhibited or functionally insufficient, upstream signals from TNFR1, FAS, or TLRs can promote the formation of the RIPK1–RIPK3 necrosome, which subsequently induces MLKL phosphorylation, oligomerization, and translocation to the plasma membrane. This ultimately disrupts membrane integrity, leading to cell lysis and the release of DAMPs. Because necroptosis is accompanied by the release of ATP, HMGB1, inflammatory cytokines, and chemokines, it serves not only as a mode of cell death but also as a critical bridge linking tumor cell lysis, inflammatory responses, and antitumor immune activation [38-39].

ICD-associated signals, including ATP, HMGB1, and surface-exposed CRT, which facilitate dendritic cell recruitment, phagocytosis of dying cells, antigen uptake, and antigen presentation. Necroptosis is also accompanied by secondary release of cytokines and chemokines, such as IL-1α and the chemokines CXCL1 and CXCL2, which promote the activation and recruitment of immune cells (e.g., macrophages) via IL-1R and CXCR2 receptors, respectively [40]. Concurrently, NF-κB signaling activation and type I IFN production further amplify the inflammatory response, support macrophage polarization toward an M1-like phenotype, and promote NK cell and T cell activation [41]. Consequently, under appropriate conditions, necroptosis can convert an immunosuppressive tumor microenvironment into a more inflammatory and immunogenic state. However, its immunological effects are context-dependent; sustained or excessive necroptotic inflammation may drive chronic inflammation, aberrant myeloid cell recruitment, and tumor progression.

The therapeutic value of necroptosis lies in its ability to bypass apoptosis resistance. By inducing lytic cell death, it enhances tumor antigen release and local inflammation, thereby increasing tumor immunogenicity. Kim S, et al. [42] developed a porous silica nanocage system for RIPK3 mRNA delivery, which activated p-MLKL, induced necroptosis and DAMP release, promoted $CD8^+$ T cell infiltration and M1 TAM polarization, and enhanced tumor inhibition in mouse tumor models. In addition, a multifunctional immune adjuvant based on a Fe^{3+}-shikonin metal-phenolic network (FeShik) can respond to GSH and release Fe^{2+}/shikonin, thereby inducing ICD through dual mechanisms involving ferroptosis and necroptosis [43].

3.4. Cuproptosis and ICD

Cuproptosis is a copper-dependent form of RCD closely linked to mitochondrial metabolism and proteotoxic stress. Under physiological conditions, cells maintain copper homeostasis through copper

enzymes, copper chaperones, and membrane transporters. When copper uptake is excessive or copper metabolism is dysregulated, excess copper accumulates in mitochondria and preferentially binds to lipoylated components of key tricarboxylic acid cycle enzymes, such as dihydrolipoamide S-acetyltransferase (DLAT). This leads to abnormal oligomerization and aggregation of lipoylated proteins, loss of iron-sulfur cluster proteins, mitochondrial respiratory dysfunction, ROS accumulation, and acute proteotoxic stress, ultimately resulting in cell death. Distinct from other RCD modalities, the defining features of cuproptosis are copper-dependent mitochondrial protein aggregation, iron-sulfur cluster protein loss, and collapse of energy metabolism [44-47].

Emerging evidence suggests that cuproptosis may exhibit ICD-like immunogenic features under specific induction conditions. Mitochondrial dysfunction, lipoylated protein aggregation, oxidative stress, and proteotoxic stress during cuproptosis may promote the release or exposure of ICD-related DAMPs, including surface CRT exposure, HMGB1 and ATP release, and HSP70/HSP90 upregulation [47,48]. These ICD-related signals can provide danger cues to the immune system, facilitating dendritic cell recognition of dying tumor cells and enhancing tumor antigen uptake and presentation. Recent studies indicate that cuproptosis can exhibit ICD-like features when induced by specific copper ionophores and copper-based nanomaterials [48-49].

Cuproptosis may participate in antitumor immune regulation by remodeling the tumor immune microenvironment. Bioinformatics analyses have suggested associations between cuproptosis-related gene signatures, ICD scores, immune-cell infiltration, and antitumor immune activity, indicating a potential link between cuproptosis and tumor immune regulation. Following DAMP release, dendritic cell maturation and antigen presentation are enhanced, further promoting $CD8^+$ T cell infiltration and cytotoxic T cell responses. Moreover, cuproptosis-associated mitochondrial stress and inflammatory signals may influence macrophage polarization, immunosuppressive cell infiltration, and checkpoint molecule expression, thereby shifting the immunosuppressive microenvironment toward an immune-activated state. However, these immunoregulatory effects remain tumor-type and metabolic-context dependent and may be influenced by OXPHOS dependence, hypoxia status, FDX1 expression, and copper transport capacity.

Cuproptosis offers a potential therapeutic entry point for tumor immunotherapy, particularly when combined with copper ionophores, copper-based nanomaterials, or immune adjuvants. Wang P, et al.[50] developed a copper-coordinated nano-assembly that induced cuproptosis, promoted ICD-related immune activation, reduced lactate-mediated immunosuppression, and enhanced antitumor immune responses. Wan G, et al.[51] developed a copper-based nanoplatform that synergized cuproptosis induction with TLR7/8 agonist-mediated immune activation, thereby enhancing immune memory and suppressing both primary and distant tumors.

3.5. Disulfidptosis and ICD

In 2023, Liu X, et al. [52] reported a novel form of RCD driven by disulfide stress in SLC7A11-high cells under glucose starvation conditions, termed disulfidptosis. Mechanistically, glucose deprivation limits cellular reducing capacity, whereas high SLC7A11 activity promotes cystine uptake and disulfide accumulation, leading to disulfide stress, actin cytoskeleton contraction, cytoskeletal collapse, and cell death.

Current evidence suggests that disulfidptosis may be accompanied by ICD-like signals, although direct proof that it fully meets the established criteria for ICD remains limited. During disulfidptosis, disulfide stress and cytoskeletal collapse cause structural disruption of the cell, accompanied by the release of HMGB1 and ATP as well as CRT exposure—signals typically associated with ICD. Studies employing strategies such as glucose transporter inhibition, SLC7A11-dependent enhancement of cystine uptake, or disruption of redox homeostasis have successfully induced disulfidptosis in models of triple-negative breast cancer, hepatocellular carcinoma, and glioblastoma. These studies observed enhanced tumor cell immunogenicity, upregulation of antigen presentation-related signals, and increased immune cell infiltration. Thus, the key to disulfidptosis-induced ICD may not lie in cell

death itself, but in the cell structural collapse jointly driven by glucose deprivation and disulfide stress, which enables dying tumor cells to release danger signals recognizable by the immune system.

The relationship between disulfidptosis and the tumor immune microenvironment remains complex and context-dependent. Bioinformatics studies have associated disulfidptosis-related gene signatures with immune infiltration, immunosuppressive features, and patient prognosis [53]. In some tumors, high disulfidptosis-related activity is linked to reduced $CD8^+$ T cell infiltration and relative enrichment of TAMs or Tregs, suggesting an association with an immunosuppressive metabolic state. In contrast, experimentally induced disulfidptosis may promote DAMP release, dendritic cell activation, and antitumor immune responses. Therefore, disulfidptosis-related gene signatures should not be directly equated with therapeutically induced ICD-like cell death, and their immune effects require tumor-type-specific validation.

Disulfidptosis provides a new therapeutic avenue for overcoming tumor metabolic adaptation and enhancing immunotherapy. Therapeutic strategies targeting SLC7A11 or GLUT can selectively induce disulfidptosis in high-risk tumors; when combined with immune checkpoint blockade, they can enhance efficacy by remodeling the immunosuppressive tumor microenvironment. One study constructed a Pd_2Sn@GOx-SP nanosystem [54] that consumes glucose through glucose oxidase and amplifies oxidative stress, thereby inducing both caspase-1/GSDMD-dependent pyroptosis and cystine accumulation-mediated disulfidptosis. This dual-death strategy promoted HMGB1 release, CRT exposure, ATP efflux, dendritic cell maturation, and T cell infiltration. Another study developed a sonodynamic nanoplatform loaded with the GLUT1 inhibitor Bay-876, which restricted glucose uptake, exacerbated reductive insufficiency and disulfide stress in SLC7A11-high tumor cells, and enhanced ICD-like immune activation [55]. These findings suggest that disulfidptosis induction may be combined with metabolic intervention, sonodynamic therapy, or immune checkpoint blockade to enhance antitumor immunity.

3.6. Common Mechanisms and Differences Among Different RCD Forms in Promoting ICD-Related Immunogenicity

Pyroptosis, necroptosis, ferroptosis, cuproptosis, and disulfidptosis may enhance the immunogenicity of tumor cell death under specific conditions through processes such as DAMP release, inflammatory signal activation, oxidative stress, organelle damage, or metabolic stress. Based on the primary sources and release patterns of immunogenic signals induced by these RCD modalities, their mechanistic features can be categorized into four patterns: membrane damage-dominant, oxidative damage-dominant, organelle stress and proteotoxic stress-dominant, and redox imbalance and cytoskeletal collapse-dominant.

1) Membrane Damage-Dominant Type: Pyroptosis and Necroptosis

Pyroptosis and necroptosis represent membrane damage-dominant RCD modalities, in which gasdermin-mediated pore formation or MLKL-mediated membrane rupture enables rapid DAMP release and inflammatory immune activation [12,56].

2) Oxidative Damage-Dominant Type: Ferroptosis

Ferroptosis represents an oxidative damage-dominant modality, in which lipid peroxidation-derived stress signals and delayed membrane disruption may generate stage-dependent ICD-like effects [57-58].

3) Organelle Stress and Proteotoxic Stress-Dominant Type: Cuproptosis

Cuproptosis represents an organelle and proteotoxic stress-dominant modality, in which copper-dependent mitochondrial dysfunction and lipoylated protein aggregation may promote ICD-related stress signaling [59].

4) Redox Imbalance and Structural Collapse-Dominant Type: Disulfidptosis

Disulfidptosis represents a potential redox imbalance and cytoskeletal collapse-dominant modality, but its evidence as a bona fide ICD-inducing process remains comparatively limited [60].

4. Outlook and Conclusion

From an application perspective, RCD-associated ICD-like strategies may serve as useful combination partners for immune checkpoint inhibitors, radiotherapy, chemotherapy, photodynamic therapy, sonodynamic therapy, and metabolism-targeted therapies. Rational induction of ferroptosis, pyroptosis, necroptosis, cuproptosis, or disulfidptosis may help improve therapeutic responses in poorly inflamed or treatment-resistant tumors, especially those with low immunogenicity, limited T cell infiltration, or poor responsiveness to PD-1/PD-L1 blockade. With advances in nanodelivery systems and tumor microenvironment-responsive platforms, RCD inducers may achieve more selective tumor accumulation and controlled activation, thereby enhancing tumor cell killing and antitumor immune responses.

However, the clinical translation of RCD-associated ICD-like strategies still faces several challenges. RCD-induced immunogenicity is highly context-dependent, and cell death itself does not necessarily indicate functional ICD or durable antitumor immunity. In addition, excessive or persistent inflammation may cause tissue damage, recruit immunosuppressive myeloid cells, or promote tumor progression. Future studies should optimize delivery systems, dose windows, and combination sequences, while establishing biomarkers for patient selection, efficacy prediction, and safety monitoring. More importantly, standardized functional assays are needed to confirm whether these RCD modalities truly induce dendritic cell activation, antigen cross-presentation, $CD8^+$ T cell responses, immune memory, and safe in vivo antitumor efficacy.

References

[1] Bertucci A, Taleb K, Billon E, et al. A comprehensive review of mechanisms underlying resistance to immune checkpoint inhibitors. Frontiers in Immunology, 2026, 17: 1735741.

[2] Zhou Z, Mao Z, Li H, et al. Mechanistic insights and therapeutic innovation in immune-related adverse events. International Immunopharmacology, 2026, 182: 116801.

[3] Wijnen S C M A, Dimitriadis P, Wessels L F A, et al. From prediction to precision: Biomarker discovery and predictive modeling for personalized immune checkpoint blockade therapy. European Journal of Cancer, 2026, 239: 116711.

[4] Kim S Y. Immunotherapy for microsatellite-stable colorectal cancer: overcoming resistance and exploring novel therapeutic strategies. Annals of Coloproctology, 2026, 42(1): 47.

[5] He X, Xu C. Immune checkpoint signaling and cancer immunotherapy. Cell Research, 2020, 30(8): 660-669.

[6] Wojtukiewicz M Z, Rek M M, Karpowicz K, et al. Inhibitors of immune checkpoints—PD-1, PD-L1, CTLA-4—new opportunities for cancer patients and a new challenge for internists and general practitioners. Cancer and Metastasis Reviews, 2021, 40(3): 949-982.

[7] Tesniere A, Panaretakis T, Kepp O, et al. Molecular characteristics of immunogenic cancer cell death. Cell Death & Differentiation, 2008, 15(1): 3-12.

[8] Krysko D V, Garg A D, Kaczmarek A, et al. Immunogenic cell death and DAMPs in cancer therapy. Nature Reviews Cancer, 2012, 12(12): 860-875.

[9] Li Z, Lai X, Fu S, et al. Immunogenic cell death activates the tumor immune microenvironment to boost the immunotherapy efficiency. Advanced Science, 2022, 9(22): 2201734.

[10] Mao C, Wang M, Zhuang L, et al. Metabolic cell death in cancer: Ferroptosis, cuproptosis, disulfidptosis, and beyond. Protein & Cell, 2024, 15(9): 642-660.

[11] Galluzzi L, Kepp O, Zitvogel L, et al. Cancer cell death: Cell-autonomous and immunogenic dimensions. Cancer Cell, 2026, 44(2): 281-305.

[12] Galluzzi L, Kepp O, Hett E, et al. Immunogenic cell death in cancer: Concept and therapeutic implications. Journal of Translational Medicine, 2023, 21(1): 162.

[13] Eskandani N A, Ghasemzaei M, Farani M R, et al. Engineering ER-stress–driven immunogenic cell death with nanomedicine: UPR-axis control, DAMP signaling, and clinical translation. Nano Today, 2026, 69: 103065.

[14] Fucikova J, Kepp O, Kasikova L, et al. Detection of immunogenic cell death and its relevance for cancer therapy. Cell Death & Disease, 2020, 11(11): 1013.

[15] Garg A, Dudek-Peric A M, Romano E, et al. Immunogenic cell death. The International Journal of Developmental Biology, 2015, 59(1): 131-140.

[16] Nace G, Evankovich J, Eid R, et al. Dendritic cells and damage-associated molecular patterns: endogenous danger signals linking innate and adaptive immunity. Journal of Innate Immunity, 2011, 4(1): 6-15.

[17] Boaru D L, Fraile-Martinez O, De Castro-Martinez P, et al. What is—and What is not—Immunogenic cell death? Functional definitions, experimental standards, and common pitfalls. International Journal of Molecular Sciences, 2026, 27(7): 3061.

[18] Zhang H, Li S, Liu S, et al. Therapeutic targeting of cell death-immune crosstalk in cancer to rewire the tumor immune microenvironment. Molecular Cancer, 2025, 24(1): 1-36.

[19] Zhu S, Wang Y, Tang J, et al. Radiotherapy induced immunogenic cell death by remodeling tumor immune microenvironment. Frontiers in Immunology, 2022, 13: 1074477.

[20] Wang W, Green M, Choi J E, et al. $CD8^+$ T cells regulate tumour ferroptosis during cancer immunotherapy. Nature, 2019, 569(7755): 270-274.

[21] Zhang Z, Zhang Y, Xia S, et al. Gasdermin E suppresses tumour growth by activating anti-tumour immunity. Nature, 2020, 579(7799): 415-420.

[22] Liang Y, Zhao Y, Qi Z, et al. Ferroptosis: $CD8^+$ T cells' blade to destroy tumor cells or poison for self-destruction. Cell Death Discovery, 2025, 11(1): 128.

[23] Deng W, Shang H, Tong Y, et al. The application of nanoparticles-based ferroptosis, pyroptosis and autophagy in cancer immunotherapy. Journal of Nanobiotechnology, 2024, 22(1): 97.

[24] Tang R, Xu J, Zhang B, et al. Ferroptosis, necroptosis, and pyroptosis in anticancer immunity. Journal of Hematology & Oncology, 2020, 13(1): 110.

[25] Dixon S J, Lemberg K M, Lamprecht M R, et al. Ferroptosis: An iron-dependent form of nonapoptotic cell death. Cell, 2012, 149(5): 1060-1072.

[26] Catanzaro E, Feron O, Skirtach A G, et al. Immunogenic cell death and role of nanomaterials serving as therapeutic vaccine for personalized cancer immunotherapy. Frontiers in Immunology, 2022, 13: 925290.

[27] Wiernicki B, Maschalidi S, Pinney J, et al. Cancer cells dying from ferroptosis impede dendritic cell-mediated anti-tumor immunity. Nature Communications, 2022, 13(1): 3676.

[28] Kapralov A A, Yang Q, Dar H H, et al. Redox lipid reprogramming commands susceptibility of macrophages and microglia to ferroptotic death. Nature Chemical Biology, 2020, 16(3): 278-290.

[29] Bao Y, Li G, Li S, et al. A novel nanomedicine integrating ferroptosis and photothermal therapy, well-suitable for PD-L1-mediated immune checkpoint blockade. Materials Today Bio, 2024, 29: 101346.

[30] Peng H, Chang A Q, Zhang H, et al. A novel biomimetic nanoplatform amplifies ferroptosis for specific cGAS-STING pathway activation to enhance hepatocellular carcinoma chemo-immunotherapy[J]. Journal of Nanobiotechnology, 2025.

[31] Hou J, Hsu J M, Hung M C. Molecular mechanisms and functions of pyroptosis in inflammation and antitumor immunity. Molecular Cell, 2021, 81(22): 4579-4590.

[32] Tsuchiya K. Switching from apoptosis to pyroptosis: Gasdermin-elicited inflammation and antitumor immunity. International Journal of Molecular Sciences, 2021, 22(1): 426.

[33] Casagrande Raffi G, Chen J, Feng X, et al. An antibiotic that mediates immune destruction of senescent cancer cells. Proceedings of the National Academy of Sciences, 2024, 121(52): e2417724121.

[34] Oresta B, Pozzi C, Braga D, et al. Mitochondrial metabolic reprogramming controls the induction of immunogenic cell death and efficacy of chemotherapy in bladder cancer. Science Translational Medicine, 2021, 13(575): eaba6110.

[35] Zhou Z, He H, Wang K, et al. Granzyme A from cytotoxic lymphocytes cleaves GSDMB to trigger pyroptosis in target cells. Science, 2020, 368(6494): eaaz7548.

[36] Wang Q, Wang Y, Ding J, et al. A bioorthogonal system reveals antitumour immune function of pyroptosis. Nature, 2020, 579(7799): 421-426.

[37] Xi G, Gao J, Wan B, et al. GSDMD is required for effector $CD8^+$ T cell responses to lung cancer cells. International Immunopharmacology, 2019, 74: 105713.

[38] Chen K S, Manoury-Battais S, Kanaya N, et al. An inducible RIPK3-driven necroptotic system enhances cancer cell–based immunotherapy and ensures safety. The Journal of Clinical Investigation, 2025, 135(2).

[39] Morgan M J, Kim Y S. Roles of RIPK3 in necroptosis, cell signaling, and disease. Experimental & Molecular Medicine, 2022, 54(10): 1695-1704.

[40] Munoz-Wolf N, Ward R W, Hearnden C H, et al. Non-canonical inflammasome activation mediates the adjuvanticity of nanoparticles. Cell Reports Medicine, 2023, 4(1): 100899.

[41] Yatim N, Cullen S, Albert M L. Dying cells actively regulate adaptive immune responses. Nature Reviews Immunology, 2017, 17(4): 262-275.

[42] Kim S, Kim S, Kim S, et al. Improvement of therapeutic effect via inducing non-apoptotic cell death using mRNA-protection nanocage. Advanced Healthcare Materials, 2024, 13(27): e2400240.

[43] Feng W, Shi W, Cui Y, et al. Fe(III)-Shikonin supramolecular nanomedicines as immunogenic cell death stimulants and multifunctional immunoadjuvants for tumor vaccination. Theranostics, 2023, 13(15): 5266-5289.

[44] Li J, Zhang G, Sun Z, et al. Immunogenic cuproptosis in cancer immunotherapy via an in situ cuproptosis-inducing system. Biomaterials, 2025, 319: 123201.

[45] Xiong C, Ling H, Hao Q, et al. Cuproptosis: p53-regulated metabolic cell death? Cell Death & Differentiation, 2023, 30(4): 876-884.

[46] Tsvetkov P, Coy S, Petrova B, et al. Copper induces cell death by targeting lipoylated TCA cycle proteins. Science, 2022, 375(6586): 1254-1261.

[47] Luo Y, Luo X, Ru Y, et al. Copper (II)-based nano-regulator correlates cuproptosis burst and sequential immunogenic cell death for synergistic cancer immunotherapy. Biomaterials Research, 2024, 28: 39.

[48] Guan M, Cheng K, Xie X T, et al. Regulating copper homeostasis of tumor cells to promote cuproptosis for enhancing breast cancer immunotherapy. Nature Communications, 2024, 15(1): 10060.

[49] Wu X, Zhang S, Feng M, et al. Glutathione induced in situ activation of dual-locked cuproptosis nanoamplifier with glycolysis metabolism inhibition to boost cancer immunotherapy. Advanced Healthcare Materials, 2025, 14(4): 2403380.

[50] Wang P, Guo W, Liu S, et al. Novel Pt@ PCN-Cu-induced cuproptosis amplifies αPD-L1 immunotherapy in pancreatic ductal adenocarcinoma through mitochondrial HK2-mediated PD-L1 upregulation. Journal of Experimental & Clinical Cancer Research, 2025, 44(1): 149.

[51] Wan G, Chen J, Zhou Y, et al. Light-cured millineedle platform delivers “nano-pomegranate” for combinatorial electrodynamic therapy and cuproptosis against oral carcinoma. Bioactive Materials, 2025, 53: 718-736.

[52] Liu X, Nie L, Zhang Y, et al. Actin cytoskeleton vulnerability to disulfide stress mediates disulfidptosis. Nature Cell Biology, 2023, 25(3): 404-414.

[53] Liu Z, Sun L, Zhu W, et al. Disulfidptosis signature predicts immune microenvironment and prognosis of gastric cancer. Biology Direct, 2024, 19(1): 65.

[54] Zhu Y, Wang X, Feng L, et al. Intermetallics triggering pyroptosis and disulfidptosis in cancer cells promote anti-tumor immunity. Nature Communications, 2024, 15(1): 8696.

[55] Wang K, Li L, Liang G, et al. Sonodynamic activated nanoparticles with Glut1 inhibitor and cystine-containing polymer stimulate disulfidptosis for improved immunotherapy in bladder cancer. Biomaterials, 2025, 319: 123178.

[56] Chen G, Zhang Z, Chong W, et al. The molecular mechanisms of pyroptosis and its implications in tumor immunotherapy. Molecular Cancer, 2026, 25(1): 63.

[57] Rahaman S, Vohora D, Kamal A. Ferroptosis-induced immune modulation: A new frontier in glioblastoma therapy. Naunyn-Schmiedeberg's Archives of Pharmacology, 2026, 399(7): 9411–9436.

[58] Liu Y, Chen Q, Xu J, et al. Programmed cell death in lung cancer: mechanisms, immune responses, and therapeutics. Apoptosis, 2026, 31(4): 128.

[59] Wu S, Hong Z, Zhang L. Cuproptosis: Bridging targeted therapy and immunotherapy in cancer treatment. Critical Reviews in Oncology/Hematology, 2026, 222: 105296.

[60] Zhen W, Zhao T, Chen X, et al. Unlocking the potential of disulfidptosis: Nanotechnology-driven strategies for advanced cancer therapy. Small, 2025, 21(23): 2500880.