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Death plasticity in cancer: a network perspective on regulated cell death pathways and their therapeutic exploitation

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For most of the twentieth century, apoptosis was regarded as the principal—if not sole—regulated route to cellular self-destruction, and cancer therapy was designed accordingly. Over the past decade, however, the discovery of mechanistically distinct regulated cell death (RCD) modalities—ferroptosis, pyroptosis, necroptosis, cuproptosis, disulfidptosis, PANoptosis, and a broader non-canonical landscape encompassing autophagy-dependent death, anoikis, entosis, parthanatos, and lysosomal cell death—has reframed resistance to cell death as a composite phenotype rather than a single evaded pathway. This review synthesizes the molecular executors, cancer-specific evasion mechanisms, and immunological consequences of each RCD modality, before shifting to the network level to examine the master regulatory axes (phosphoinositide 3-kinase (PI3K)–AKT–mechanistic target of rapamycin (mTOR), nuclear factor erythroid 2-related factor 2 (NRF2)–Kelch-like ECH-associated protein 1 (KEAP1), p53, and Wnt/β-catenin) and metabolic reprogramming events (the Warburg shift) through which single oncogenic alterations confer broad-spectrum death resistance. Particular attention is given to the immunogenicity of different death modalities within the tumor microenvironment, where lytic pathways that release damage-associated molecular patterns (DAMPs), such as necroptosis, pyroptosis, and cuproptosis, can convert immunologically cold tumors into those responsive to checkpoint blockade, in contrast to the immunologically silent execution of apoptosis. The review concludes by identifying the principal barriers to clinical translation—context-dependent death sensitivity, a scarcity of validated pharmacological probes for non-apoptotic pathways, contradictory immunological findings, tumor metabolic heterogeneity, and the absence of standardized clinical biomarkers—and outlines emerging directions, including proteolysis-targeting chimera (PROTAC)-based degradation of resistance nodes, composite multi-pathway death signatures, and single-cell/spatial approaches capable of resolving death competence at cellular resolution. Understood as a plastic, network-level capability rather than a switch to be thrown, cancer cell death offers a substantially larger and more combinable therapeutic target space than the apoptosis-centric paradigm alone.

KEYWORDS
cancer death plasticity, cuproptosis, disulfidptosis, ferroptosis, immunogenic cell death

Introduction: from cell death morphology to regulated death networks

For most of the twentieth century, cell death was framed as a dualism: cells either died accidentally through physical disruption, toxin exposure, or irreversible necrosis, or executed an intrinsically encoded self-dissolution program that Kerr, Wyllie, and Currie named apoptosis in 1972 [1]. This model was morphologically tractable, genetically addressable, and therapeutically attractive, and for decades seemed to explain the central logic of cell death. Restoring apoptosis in cancer cells therefore appeared a coherent route to tumor elimination. Three decades of productive research produced molecular atlases of caspase cascades, B-cell lymphoma 2 (BCL-2) family interactions, and death-receptor signaling, establishing the foundation of contemporary oncology. Yet clinical experience exposed persistent inadequacy—not because the science was wrong, but because it was incomplete [2, 3]. Cancer cells had not simply learned to resist one program; they had reorganized their biology around evading cellular self-destruction broadly, while apoptosis-centered therapy targeted only the visible fraction of a larger, interconnected system. The framework's appeal lay in its tractable morphology, addressable genetics, and therapeutic promise.

Over the past 15 years, the field has recognized regulated cell death as a network of mechanistically distinct, molecularly individuated yet functionally interconnected modalities, each an evolutionarily conserved response to defined stress, controlled by dedicated executors and checkpoints, and differentially altered in cancer [4]. Under Nomenclature Committee on Cell Death (NCCD) recommendations, "regulated cell death" (RCD) is initiated by signaling modules amenable to pharmacological or genetic modulation; "programmed cell death" (PCD) denotes RCD in strictly physiological settings, such as development or tissue turnover [5]. The RCD catalogue now includes ferroptosis, marked by iron-dependent lipid peroxidation and GPX4 inactivation; pyroptosis, executed by gasdermin family pore-forming proteins after inflammasome activation; necroptosis, often mediated by receptor-interacting protein kinase 3 (RIPK3)–mixed lineage kinase domain-like protein (MLKL) when caspase-8 is insufficient; cuproptosis, caused by copper-induced aggregation of lipoylated mitochondrial proteins; disulfidptosis, triggered by actin-cytoskeletal collapse under cystine-driven disulfide stress; and PANoptosis, which engages pyroptotic, apoptotic, and necroptotic machinery through a scaffolded PANoptosome complex [6–8]. Other modalities include autophagy-dependent death, anoikis, entosis, parthanatos, and lysosomal membrane permeabilization-driven death, each contributing to the suppression of malignant growth under physiological conditions and subject to cancer-specific exploitation or circumvention [9, 10]. Their shared feature is regulated timing, magnitude, and consequence, making them, in principle, pharmacologically accessible (Figure 1).

This expanded taxonomy changes cancer biology rather than merely adding categories. Each RCD modality has dedicated evasion mechanisms, revealing "resistance to cell death" as a composite phenotype assembled through the simultaneous, coordinately maintained suppression of more than a dozen death programs [9]. A small set of master axes organizes this architecture: PI3K-AKT-mTOR, the NRF2-KEAP1 antioxidant transcriptional program, the p53 tumor suppressor network, and epigenetic machinery controlling DNA methylation and histone modification. Each axis simultaneously influences vulnerability across several death pathways, so single oncogenic alterations at these hubs produce broad-spectrum resistance whose scope is underestimated by single-pathway analyses [9–11]. The Warburg shift toward aerobic glycolysis and suppressed oxidative phosphorylation is likewise more than a biosynthetic adaptation; it attenuates mitochondria-dependent and redox-sensitive programs, including cuproptosis, disulfidptosis, and ferroptosis, which require oxidative metabolism for execution [7]. Metabolic identity and death resistance therefore reflect the same underlying reprogramming rather than independent cancer phenotypes. These hubs can therefore protect against several death triggers through one oncogenic change.

Death modality also determines immunological outcome and treatment response, with major implications for cancer therapy. Apoptosis, through orderly membrane packaging and anti-inflammatory "find-me" and "olerate-me" signals, is predominantly immunologically silent. Thus, the extensive apoptotic death induced by conventional chemotherapy can remain invisible to adaptive immunity, limiting the durable antitumor response that treatment might otherwise generate [12, 13]. Pyroptosis, necroptosis, and cuproptosis are intrinsically lytic and immunogenic, releasing DAMPs such as calreticulin, high-mobility group box 1 (HMGB1), and adenosine triphosphate (ATP); these activate dendritic cells, promote cross-priming of tumor-antigen-specific $CD8^+$ T lymphocytes, and render immunologically cold tumors susceptible to immune checkpoint blockade [13]. Therapy therefore aims not only to kill cancer cells but to do so in ways that generate durable immunity—an *in situ* vaccine against residual and metastatic disease [12]. This stratification reframed the therapeutic goal: how cancer cells are killed matters as much as whether they die.

Against this background, this review examines the molecular mechanisms, cancer-specific evasion strategies, and therapeutic implications of major RCD modalities. It is organized to illuminate each pathway's biology while emphasizing network-level principles emerging from interactions among pathways. The canonical apoptosis section defines the mechanistic and resistance landscape for subsequent pathways. Pyroptosis, necroptosis, and PANoptosis are examined together as immunogenic inflammatory deaths whose coordinated suppression reveals shared upstream regulation. Ferroptosis receives particular attention in therapy-resistant mesenchymal cancer states, a relationship that has yielded some of the most promising therapeutic findings in recent cell-death research. Cuproptosis and disulfidptosis are assessed as recently characterized metabolic RCDs that expose specific copper and redox vulnerabilities and already show evolved resistance. Autophagy-dependent death, anoikis, entosis, parthanatos, and lysosomal cell death are addressed in their specific biological contexts and as sources of death plasticity. The review then analyzes network-level crosstalk and shared nodes through which cancer achieves multipathway resistance, followed by the immunological consequences of death selection in the tumor microenvironment as determinants of immunotherapy

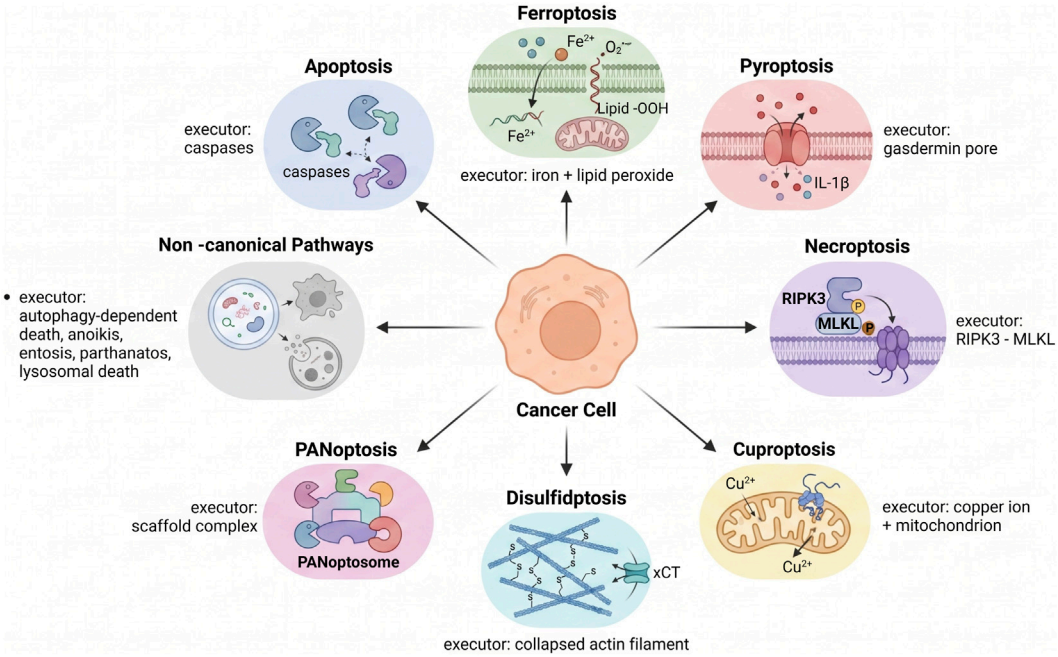


FIGURE 1
Major regulated cell death pathways in cancer. Schematic overview of apoptosis, ferroptosis, pyroptosis, necroptosis, cuproptosis, disulfidptosis, PANoptosis, and selected non-canonical cell death mechanisms, highlighting their principal molecular executors and cellular effectors.

responsiveness with direct clinical implications. It concludes by integrating evasion across modalities, surveying therapies that exploit regulated-death network logic, and identifying the scientific and translational challenges that must be solved to convert mechanistic richness into durable clinical benefit. The organizing principle is that cancer death is not a switchable program but a plastic, network-level capability requiring network-level therapeutic intelligence.

Apoptosis: the canonical therapeutic death pathway and cancer resistance

Apoptosis is central to cancer biology and treatment: it eliminates damaged, superfluous, or genomically unstable cells in normal tissues; mediates killing by the vast majority of chemotherapeutic agents, targeted kinase inhibitors, and ionizing radiation; and is the most extensively and multiply co-opted death program in malignancy [3]. This dual role—as principal tumor-suppressive mechanism and primary target of cancer's deeply ingrained survival adaptations—creates the apoptosis paradox: cancers with high constitutive apoptotic activity, reflecting ongoing selection pressure, evolve especially sophisticated and redundant resistance machinery [2]. Understanding this paradox is essential for explaining why apoptosis-centered therapies fail and for framing the broader death plasticity underlying therapeutic resistance. It is a prerequisite for understanding death plasticity across malignancies.

Apoptosis follows two distinct but convergent routes. The intrinsic (mitochondrial) pathway responds to DNA damage, oncogene activation, growth-factor withdrawal, or oxidative injury. BCL-2 family proteins govern mitochondrial outer membrane permeabilization (MOMP), releasing cytochrome c into the cytoplasm, where it binds apoptotic peptidase activating factor 1 (APAF1) to form the apoptosome and activate caspase-9. MOMP also releases second mitochondria-derived activator of caspases (SMAC; also known as DIABLO), which is not an apoptosome component but antagonizes inhibitor of apoptosis proteins (IAPs), enabling executioner caspases-3, -6, and -7 [14]. The extrinsic pathway begins when Fas ligand (FasL), tumor necrosis factor alpha (TNF-α), or TNF-related apoptosis-inducing ligand (TRAIL) binds a cognate transmembrane death receptor. Adaptor recruitment forms the death-inducing signaling complex (DISC) and activates caspase-8, which directly cleaves executioner caspases or, in type II cells requiring signal amplification, engages mitochondria through BID cleavage (Figure 2) [15]. Both routes converge on caspase-3, whose ordered cleavage of hundreds of structural, regulatory, and metabolic substrates produces membrane blebbing, chromatin condensation, DNA laddering, and phagocytosed apoptotic bodies without inflammation [16]. This immunological quietude contrasts with inflammatory lytic deaths: tumor apoptosis is cytotoxic but does not necessarily activate immunity against residual disease [13]. The intrinsic route is also termed the mitochondrial pathway, whereas the extrinsic route is receptor initiated. Their distinct initiating signals nevertheless converge on a common execution phase.

The BCL-2 family centrally regulates the intrinsic pathway and provides the molecular terrain on which cancer cells enact apoptotic resistance [17, 18]. It comprises anti-apoptotic multidomain proteins BCL-2, BCL-XL, MCL-1, BCL-W, and BFL-1/A1, which promote survival by sequestering pro-apoptotic members; multidomain pro-apoptotic effectors BAX and BAK, which

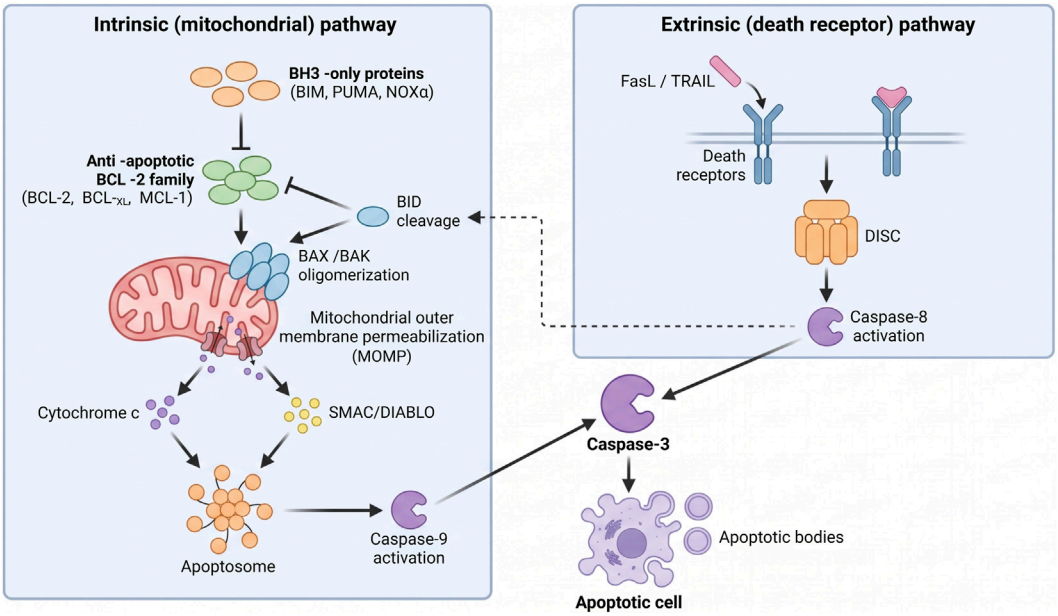


FIGURE 2
Intrinsic and extrinsic apoptotic pathways and their convergence on caspase-3. In the intrinsic (mitochondrial) pathway, BH3-only proteins (BIM, PUMA, and NOXA) inhibit anti-apoptotic BCL-2 family members (BCL-2, BCL-XL, and MCL-1), permitting BAX/BAK oligomerization and mitochondrial outer membrane permeabilization (MOMP). The release of cytochrome *c* promotes apoptosome formation and caspase-9 activation, which in turn activates caspase-3. In the extrinsic (death receptor) pathway, FasL or TRAIL binding induces death-inducing signaling complex (DISC) formation and caspase-8 activation. Caspase-8 can directly activate caspase-3 and cleave BID, thereby linking the extrinsic and intrinsic pathways. Caspase-3 activation leads to apoptotic cell dismantling and apoptotic body formation. Solid arrows indicate pathway progression; the T-bar indicates inhibition, and the dashed arrow denotes caspase-8-mediated BID cleavage.

execute MOMP upon activation; and BH3-only sensors BIM, PUMA, NOXA, BID, and BAD, which respond to stress by activating BAX/BAK or neutralizing anti-apoptotic proteins [14]. BH3 profiling measures mitochondrial priming, or dependence on anti-apoptotic function: highly primed cells contain activating BH3 peptides held in check by anti-apoptotic proteins and are exquisitely sensitive to pharmacological disruption, whereas unprimed cells lack this activating load and resist death regardless of anti-apoptotic expression [17].

Priming varies across and within cancers and predicts BH3-mimetic sensitivity, an insight translated by venetoclax, a BCL-2-selective BH3 mimetic that has transformed treatment of chronic lymphocytic leukemia and acute myeloid leukemia. By displacing BIM and other activating proteins from BCL-2, venetoclax triggers MOMP in highly primed hematological malignancies [14]. Resistance arises through MCL-1 or BCL-XL upregulation, BCL-2 binding-site mutations such as G101V, or loss of pro-apoptotic proteins that lowers activating load independently of anti-apoptotic targeting [19]. MCL-1 is genomically amplified in a substantial fraction of human cancers and its protein is stabilized by oncogenic signaling through mitogen-activated protein kinase (MAPK) and PI3K–AKT; it is therefore a leading mediator of intrinsic and acquired BH3-mimetic resistance, motivating selective MCL-1 inhibitors now advancing in clinical trials [18, 19]. This has driven intensive efforts to develop selective MCL-1 inhibitors.

p53 is the most consequential transcriptional activator of intrinsic apoptosis. Its loss in approximately half of human malignancies allows simultaneous escape from DNA damage-induced cell-cycle arrest, senescence, and apoptosis [20]. After genotoxic stress, wild-type p53 induces PUMA, NOXA, BAX, and BID, represses BCL-2 and BCL-XL, and shifts the BCL-2 rheostat decisively toward MOMP. Cytoplasmic p53 also directly engages BCL-XL and BCL-2; Wei et al. structurally characterized this interaction at atomic resolution, showing that p53's DNA-binding domain inserts two loops into their BH3-binding grooves and competes with pro-apoptotic ligands. TP53 mutations can additionally confer dominant gain-of-function interactions that drive proliferation, metabolic reprogramming, epithelial-to-mesenchymal transition (EMT), and immune evasion, converting a tumor suppressor into an oncogenic driver with adverse prognostic implications [21]. Constitutive PI3K-AKT-mTOR activation, caused by PIK3CA mutations, PTEN loss, or receptor tyrosine kinase amplification across solid tumors, suppresses apoptosis: AKT inactivates BAD and caspase-9 by phosphorylation, stabilizes MDM2 to promote p53 degradation, and activates nuclear factor kappa B (NF-κB), inducing BCL-2, BCL-XL, and IAPs [11, 22]. IAPs—including X-linked inhibitor of apoptosis protein (XIAP), survivin (BIRC5), cellular IAP 1 (cIAP1/BIRC2), and cellular IAP 2 (cIAP2/BIRC3)—form an additional anti-apoptotic tier and directly inhibit caspases-3, -7, and -9 through baculoviral IAP repeat (BIR) domain-mediated interactions. Their natural antagonist, SMAC/DIABLO, released after MOMP, is sequestered or transcriptionally suppressed in resistant cancer cells [23]. The IAP family therefore adds a further checkpoint after mitochondrial commitment.

TRAIL remains therapeutically attractive for its remarkable selectivity toward cancer over normal cells, but clinical translation in solid tumors has been repeatedly frustrated by widespread resistance [15]. Mechanisms include downregulation or epigenetic silencing of agonistic receptors DR4 and DR5; decoy receptors that bind TRAIL without transmitting a death signal; FLICE-inhibitory protein (FLIP) isoforms that compete with caspase-8 for DISC recruitment and block initiation; and high-level BCL-XL or MCL-1 in type II cells, which require mitochondrial amplification [15]. Resistance also reflects cell biology rather than canonical circuitry, including anoikis resistance—the acquired ability to survive extracellular-matrix detachment. In normal epithelium, detachment withdraws integrin-dependent survival signaling and triggers anoikis; cancer cells evade it by increasing anti-apoptotic BCL-2 proteins, activating integrin-independent PI3K–AKT, and undergoing EMT-associated transcriptional reprogramming [24]. RNA-splicing dysregulation adds another layer: cancer-associated alternative splicing generates truncated or isoform-switched apoptotic proteins, including pro-survival BCL-XL over pro-apoptotic BCL-XS and anti-apoptotic MCL-1L over shorter isoforms, systematically biasing the BCL-2 rheostat without mutation [25]. Together, BCL-2-family overexpression, gain-of-function p53 mutation, PI3K-AKT-mTOR hyperactivation, IAP upregulation, death-receptor silencing, anoikis resistance, and splicing-driven switching form a mutually reinforcing shield. This ensemble explains the initial inadequacy of cytotoxic regimens and the near-universal acquired resistance underlying relapse, while identifying nodes to restore apoptosis or redirect cells to alternative death programs [26]. These layers operate at distinct points and couple pathway defects with cell-state plasticity.

Inflammatory cell death programs: pyroptosis, necroptosis, and PANoptosis

Over the past decade, regulated cell death research has established that inflammatory modalities—pyroptosis, necroptosis, and the convergent entity PANoptosis—are central to tumor suppression, immune surveillance, and the balance between malignant growth and immune containment, not peripheral features of host defense. Unlike apoptosis, which packages cellular contents to limit immune visibility, pyroptosis and necroptosis are lytic and release damage-associated molecular patterns (DAMPs), pro-inflammatory cytokines, and intracellular alarmins that recruit and activate effector immune populations [27]. This immunogenicity makes them attractive antitumor mechanisms but also exposes them to the evasive pressures cancer cells apply to lethal signaling, creating a tumor-microenvironment tension between destruction and adaptation. They therefore remain part of the dynamic equilibrium between malignant growth and immune containment.

Pyroptosis is executed by gasdermin (GSDM) family pore-forming proteins, recognized as definitive effectors about a decade ago [6, 28]. This sequence couples intracellular danger detection to membrane permeabilization. In the canonical route, intracellular pattern-recognition receptors detect cytosolic danger signals and include NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3), NLR family pyrin domain containing 1 (NLRP1), NLR family CARD domain-containing protein 4 (NLRC4), and absent in melanoma 2 (AIM2)—assemble inflammasomes and activate caspase-1, which cleaves gasdermin D (GSDMD) to release its cytotoxic N-terminal domain [29]. The liberated GSDMD-NT binds phosphoinositides and cardiolipin in the plasma-membrane inner leaflet, then oligomerizes into large transmembrane pores approximately 10–20 nm in diameter that disrupt osmotic integrity and permit interleukin-1 beta (IL-1β) and interleukin-18 (IL-18) secretion before frank lysis [30]. In the non-canonical route, caspase-4, -5, and -11 directly sense cytosolic lipopolysaccharide and cleave GSDMD without caspase-1 [31]. Du et al. showed that mitochondria-generated reactive oxygen species (ROS) drive S-palmitoylation of GSDMD at Cys191, required for pore formation and capable of acting as a general activation switch even without proteolytic cleavage; S-palmitoylation thus provides a cleavage-independent activation route and links mitochondrial redox status directly to pyroptosis [32]. Miao et al. further showed that GSDMD pores permeabilize both the inner and outer mitochondrial membranes, allowing mitochondrial damage to amplify and sustain pyroptosis in a self-reinforcing feedforward loop [33]. Beyond GSDMD, gasdermin E (GSDME) is an alternative executor with particular relevance to cancer: caspase-3 cleavage converts otherwise silent, immunologically inert apoptosis into inflammatory lysis [34]. Promoter methylation frequently silences GSDME in cancer cells, permitting caspase-3-mediated apoptosis without the inflammatory immune recruitment that would otherwise follow. Pharmacological or epigenetic restoration of GSDME expression can therefore reactivate pyroptotic immunogenicity in otherwise immunologically cold tumors [35].

Necroptosis is executed by the RIPK3–MLKL axis, whereas receptor-interacting protein kinase 1 (RIPK1) is context-dependent and not obligatory in every setting [5, 36]. In tumor necrosis factor receptor 1 (TNFR1)-associated membrane complex I, ubiquitinated RIPK1 mainly scaffolds NF-κB-dependent survival and inflammatory programs. After complex remodeling and deubiquitination, kinase-active RIPK1 can promote RIPK3 activation and MLKL phosphorylation, oligomerization, and membrane localization when caspase-8 activity is low and RIPK3/MLKL machinery intact [37]. Caspase-8–c-FLIP can restrain necroptosis, RIPK1 can inhibit RIPK3-dependent necroptosis in some settings, and RIPK3 can respond to RIPK1-independent inputs. RIPK1 can therefore function as either a scaffold or a kinase, depending on context. Thus, caspase-8 inhibition may favor, but does not guarantee, necroptosis; permissive stimulation and intact RIPK3/MLKL machinery remain necessary [5, 38, 39]. Cancer cells evade necroptosis, notably by transcriptional silencing or epigenetic repression of RIPK3 and MLKL in colorectal, gastric, and pancreatic carcinomas. Loss of either component makes the pathway nonfunctional despite upstream activation [40]. This axis is therefore conditional, not universal. The microenvironment also regulates necroptosis: extracellular vesicles from pyroptotic cells can propagate gasdermin pores to bystander cells, including immune

effectors, spreading inflammation, while stromal necroptotic or pyroptotic events may condition immune activity as tumoricidal or immunosuppressive depending on context [41, 42].

Kanneganti et al. formalized PANoptosis as an inflammatory regulated cell death modality that engages pyroptotic, apoptotic, and necroptotic machinery in the same cell through multifaceted scaffolding complexes termed PANoptosomes [8]. These scaffolds include RIPK1, RIPK3, Fas-associated protein with death domain (FADD), caspase-8, caspase-1, NLRP3, and Z-DNA-binding protein 1 (ZBP1); stimulus-dependent composition determines the relative pyroptotic, apoptotic, and necroptotic features [43]. This integration provides redundancy: because pathogens and malignant cells can disable individual pathways, coordinated activation prevents disruption of one axis from conferring wholesale death resistance [44]. Malireddi et al. showed that tumor necrosis factor alpha (TNF-α) plus interferon gamma (IFN-γ) induces PANoptosis across diverse cancer cell lineages and suppresses tumor growth *in vivo*, linking inflammatory cytokines generated by successful immunotherapy to elimination of therapy-resistant cancer populations. PANoptosis may therefore act downstream of immune checkpoint blockade and T cell-derived cytokines, with immunotherapy efficacy potentially depending on tumor cells' ability to execute it [40]. Tumors evade PANoptosis by suppressing all three pathways: epigenetic silencing of GSDME and RIPK3 plus upregulation of anti-apoptotic BCL-2 family members creates resistance to cytokine-induced inflammatory death, while constitutive NF-κB and PI3K-AKT signaling maintains pro-survival genes that compete with PANoptosome assembly [45]. Viewing these modalities as one inflammatory death landscape rather than separate pathways reframes cancer death plasticity: durable resistance may require simultaneous disabling of multiple branches, so therapy must bypass integrated suppression.

Ferroptosis: lipid peroxidation, iron metabolism, and therapy-resistant cancer states

Dixon et al. coined ferroptosis in 2012 for an iron-dependent regulated cell death distinct biochemically and morphologically from apoptosis, necroptosis, and autophagy [46]. Since that initial description, it has accumulated one of the fastest-growing literatures among cell-death modalities [47, 48]. Its execution depends on oxidative destruction of polyunsaturated fatty acid-containing phospholipids (PUFA-PLs), driven by labile intracellular iron and reactive oxygen species that overwhelm antioxidant capacity, cause irreversible membrane damage, and kill the cell [49]. Rather than activating a dedicated executioner, ferroptosis follows failure or withdrawal of cellular guardians against lipid peroxidation; cellular antioxidant capacity is the limiting safeguard [50]. This vulnerability is particularly relevant when therapy increases antioxidant dependence. Thus, cancer cells reliant on antioxidant programs operate near the ferroptotic threshold, especially therapy-resistant and mesenchymal states.

Ferroptosis is organized around two coupled axes, lipid peroxidation and antioxidant defense: the former generates the lethal signal, whereas suppressing the latter permits death. Substrate availability determines how much peroxidation can occur, while defenses determine whether it is contained. Arachidonoyl- and adrenoyl-containing phosphatidylethanolamines (PE-PUFAs) in plasma and, critically, endoplasmic reticulum (ER) membranes are substrates; the ER is the principal site where peroxidation becomes lethal [51]. The ER localization is therefore mechanistically important, not merely anatomical. Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) esterify PUFAs into phospholipids and form a pro-ferroptotic node; high ACSL4 enriches membranes with substrates for peroxidation [52]. Ferrous iron (Fe^{2+}) catalyzes hydroxyl-radical generation through Fenton-type chemistry. Accordingly, transferrin receptor, ferritin, ferroportin, and ferritinophagy via nuclear receptor coactivator 4 (NCOA4) coordinate intracellular iron availability and thereby help determine ferroptotic sensitivity [53]. Mitochondria are dispensable in some contexts but, during cysteine depletion or aberrant oxidative phosphorylation, contribute PUFA oxidation and reactive oxygen species that amplify lipid peroxidation [54].

The principal ferroptosis defense is the glutathione peroxidase 4 (GPX4)-glutathione (GSH) axis, which reduces phospholipid hydroperoxides to alcohols and interrupts lipid-peroxidation chains [47]. GPX4 requires GSH, whose synthesis depends on cysteine imported by the System Xc^- cystine/glutamate antiporter, composed of solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2). Accordingly, System Xc^- inhibition by erastin or sorafenib depletes GSH, inactivates GPX4, and triggers ferroptosis, establishing a pharmacologically accessible cancer-death mechanism [55, 56]. At least three parallel, alternative ferroptosis-suppression defenses also operate: FSP1 (ferroptosis suppressor protein 1)–coenzyme Q10 (CoQ10), in which FSP1 regenerates ubiquinol to quench lipid radicals independently of GPX4; GTP cyclohydrolase 1 (GCH1)–tetrahydrobiopterin (BH4), which produces a membrane radical-trapping antioxidant; and dihydroorotate dehydrogenase (DHODH)–coenzyme Q (CoQ), which suppresses peroxidation in the inner mitochondrial membrane [50, 57]. Because these systems operate through distinct mechanisms and compartments, cancer cells can shift their reliance when one is targeted, helping explain the layered redundancy and incomplete *in vivo* responses to single-agent GPX4 inhibition (Figure 3). Residual defenses can thus blunt single-agent responses.

Mesenchymal and EMT-associated cancer cells, which resist conventional chemotherapy, targeted agents, and apoptosis, are consistently more ferroptosis-sensitive [47, 52]. Schwab et al. showed that the EMT transcription factor zinc finger E-box binding homeobox 1 (ZEB1) upregulates lipogenic enzymes that increase PUFA content in membrane phospholipids while reducing protective monounsaturated fatty acid-generating enzymes such as stearoyl-CoA desaturase 1 (SCD1). This ZEB1-dependent lipid reprogramming increases pro-ferroptotic substrate load in proportion to mesenchymal activation, linking the resistance phenotype directly to ferroptosis sensitivity [58]. Clinically, cells acquiring resistance to epidermal growth factor receptor (EGFR) inhibitors, platinum compounds, or taxanes through EMT-like state transitions may therefore gain marked ferroptosis sensitivity,

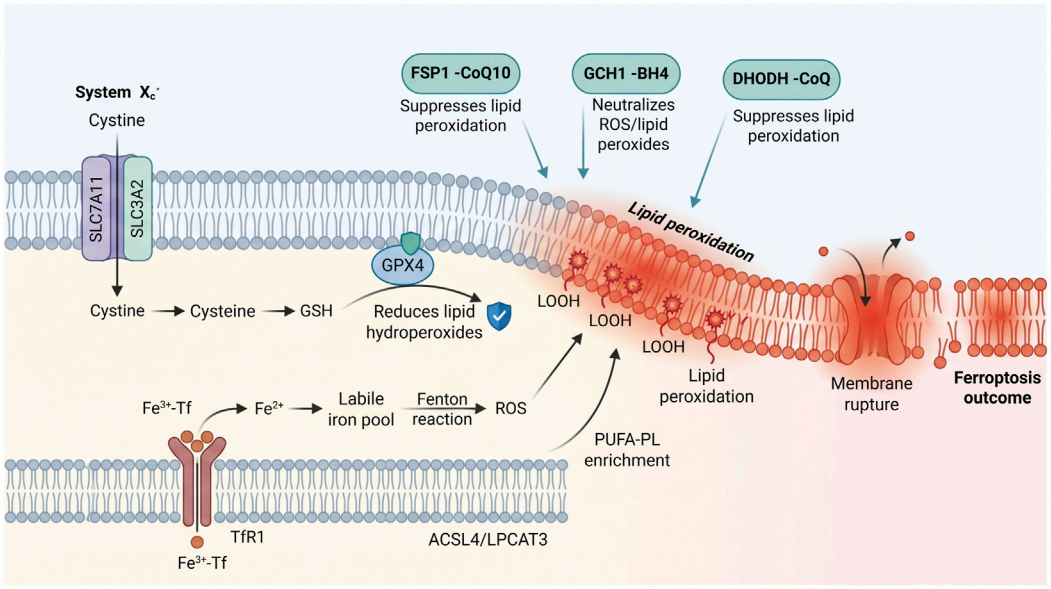


FIGURE 3
Regulation of ferroptosis by lipid peroxidation, iron metabolism, and antioxidant defense systems. System Xc^-, composed of SLC7A11 and SLC3A2, supports cystine uptake and its conversion to cysteine for glutathione (GSH) synthesis. GPX4 uses GSH to reduce lipid hydroperoxides (LOOH), limiting lipid peroxidation. In parallel, transferrin receptor 1 (TfR1)-mediated iron uptake contributes to the labile iron pool; Fe^{2+} can promote reactive oxygen species (ROS) generation through Fenton chemistry. ACSL4 and LPCAT3 promote the enrichment of polyunsaturated fatty-acid phospholipids (PUFA-PLs), increasing susceptibility to lipid peroxidation. The FSP1–CoQ_{10}, GCH1–BH_4, and DHODH–CoQ systems provide additional protection by suppressing lipid peroxidation or neutralizing ROS and lipid peroxides. When lipid peroxidation overwhelms these defenses, plasma membrane rupture and ferroptosis result. Abbreviations: GSH, glutathione; GPX4, glutathione peroxidase 4; LOOH, lipid hydroperoxide; PUFA-PL, polyunsaturated fatty-acid phospholipid; ROS, reactive oxygen species; Tf, transferrin.

creating a therapeutic window that exploits the metabolic cost of resistance [59]. Lee et al. further showed that cell-cycle arrest in therapy-resistant, slow-cycling populations suppresses ferroptosis through diacylglycerol acyltransferase (DGAT)-dependent lipid droplets, which sequester PUFAs in triacylglycerols and limit phospholipid peroxidation. Dormant cancer cells, often considered seeds of metastatic relapse, may thus gain ferroptosis resistance as a collateral consequence of proliferative quiescence; DGAT inhibition could resensitize them. This reciprocity is therapeutically exploitable.

Cancer cells employ an extensive repertoire of ferroptosis-escape mechanisms, several of which intersect canonical oncogenic pathways. In tumors with KEAP1 mutations, especially non-small cell lung cancer, constitutive NRF2 activation simultaneously upregulates SLC7A11, FSP1, thioredoxin reductase 1, heme oxygenase-1, and ferritin, creating a multi-pronged antioxidant shield and profound ferroptosis resistance [60, 61]. Koppula et al. showed that NRF2 directly targets the CoQ-FSP1 axis, which mediates ferroptosis and radiation resistance in KEAP1-deficient lung cancer, revealing a targetable downstream vulnerability. PI3K-AKT-mTOR is another resistance axis: AKT stabilizes SLC7A11, promotes sterol regulatory element-binding protein 1 (SREBP1)-driven lipogenesis that favors monounsaturated fatty acids and dilutes membrane PUFAs, and suppresses autophagic ferritin degradation, limiting catalytic iron for peroxidation [62, 63]. Wnt/β-catenin signaling independently activates GPX4 transcription, providing a direct resistance mechanism at the terminal ferroptotic effector; its hyperactivation in gastric and colorectal cancers supports chemotherapy resistance, a phenotype that co-induction of ferroptosis can reverse [64]. The microenvironment adds non-cell-autonomous protection: cancer-associated fibroblasts (CAFs) secrete exosome-derived microRNAs targeting ACSL4, suppressing PUFA enrichment in pancreatic cancer cells and conferring gemcitabine resistance [65]. These overlapping strategies span transcriptional reprogramming, kinase-mediated metabolic protection, terminal-effector maintenance, cell-cycle–lipid droplet coupling, and stromal paracrine suppression. Each can preserve viability despite an otherwise pro-ferroptotic state, showing the depth of ferroptosis plasticity and the combinatorial targeting needed for durable clinical benefit in advanced tumors.

Cuproptosis: copper metabolism, mitochondrial proteotoxicity, and cancer cell evasion strategies

Copper is an evolutionarily ancient, indispensable transition metal involved in enzymatic catalysis, mitochondrial respiration, iron metabolism, antioxidant defense, and intracellular signaling [66]. Its cycling between oxidized (Cu^{2+}) and reduced (Cu^{+}) states enables redox cofactor activity but causes acute cytotoxicity when concentrations exceed the narrow range maintained by conserved homeostatic mechanisms [67]. Tsvetkov et al. defined copper-induced cell death as cuproptosis, a regulated modality mechanistically distinct from apoptosis, necroptosis, ferroptosis,

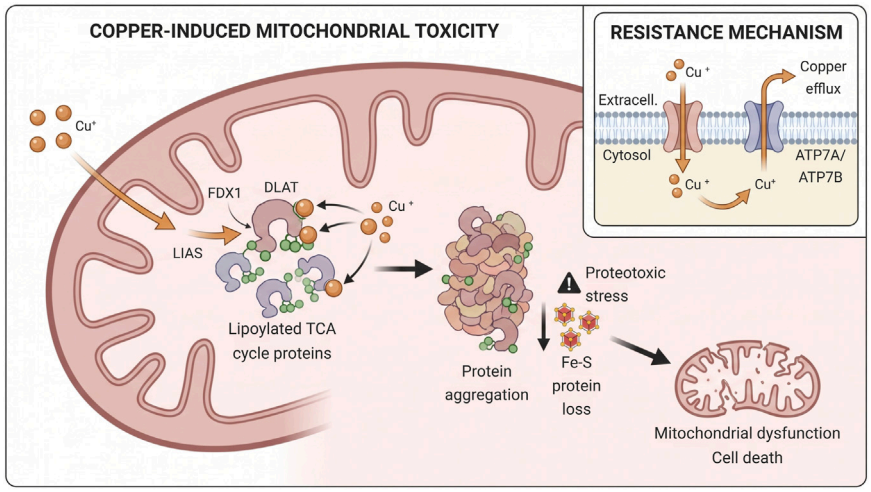


FIGURE 4
Copper-induced mitochondrial toxicity and resistance mechanisms. Copper accumulation in mitochondria promotes its binding to lipoylated tricarboxylic acid (TCA) cycle proteins, including DLAT. FDX1 and LIAS are associated with the mitochondrial protein-lipoylation pathway. Copper-induced protein aggregation and loss of iron–sulfur (Fe–S) proteins cause proteotoxic stress, mitochondrial dysfunction, and ultimately cell death. The inset illustrates a resistance mechanism in which ATP7A and ATP7B mediate copper efflux across the plasma membrane, limiting intracellular copper accumulation. Abbreviations: DLAT, dihydrolipoamide S-acetyltransferase; FDX1, ferredoxin 1; LIAS, lipoic acid synthetase; TCA, tricarboxylic acid.

and other known pathways. Their landmark *Science* study established a framework for examining cuproptosis within the broader landscape of death plasticity in malignancy.

Cuproptosis is centered in mitochondria and requires intact oxidative phosphorylation (OXPHOS). Intracellular copper accumulation—through ionophore delivery, impaired efflux, or endogenous overload—allows Cu^+ to bind lipoylated proteins in the tricarboxylic acid (TCA) cycle [68]. Key targets include dihydrolipoamide S-acetyltransferase (DLAT), a pyruvate dehydrogenase complex component, and other lipoylated enzymes; lipoic acid modification exposes their sulfur moieties to cupric coordination. Binding induces disulfide-bond-dependent aggregation and insoluble complexes that overwhelm proteostasis [69, 70]. This cascade is confined to the mitochondrial matrix, where lipoic acid synthetase (LIAS) executes lipoylation under the reducing control of ferredoxin-1 (FDX1). As the apical regulator of this machinery, FDX1 is the primary gatekeeper of cuproptosis susceptibility [71, 72]. Copper toxicity also depletes iron-sulfur (Fe-S) cluster proteins, disrupting the electron transport chain and increasing proteotoxic burden [73]. The resulting death is morphologically and biochemically distinct, with early mitochondrial dysfunction, and occurs independently of caspase activation, lipid peroxidation, or plasma membrane poration (Figure 4) [74]. This links copper sensitivity to mitochondrial localization and the metabolic state sustaining the TCA cycle. Fe-S loss is structurally distinct but functionally adjacent to aggregation and further disrupts mitochondrial respiration.

An oncologically important feature of cuproptosis is its obligate coupling to mitochondrial metabolic programming. Cells that rely predominantly on glycolysis, a phenotype pervasive in solid tumors and epitomized by the Warburg effect, are less sensitive to copper-induced proteotoxic stress than cells engaged in OXPHOS because minimizing TCA-cycle flux suppresses lipoylation [75, 76]. Thus, metabolic reprogramming that supports proliferation also partially insulates tumors from cuproptosis. Conversely, reversing the Warburg phenotype through forced mitochondrial activation or glycolytic suppression sensitizes cancer cells to copper cytotoxicity [76, 77]. This logic underlies cuproplasia, the copper-dependent dimension of tumor growth and proliferation: copper can fuel malignant expansion yet also terminate it when homeostasis fails [74, 78]. This pro-tumorigenic and tumoricidal duality defines copper biology in cancer and complicates therapy [79].

Cancer cells evade cuproptosis through molecular strategies that help explain the translational barriers to cuproptosis-based therapy. The most coherent is the Warburg shift: downregulated OXPHOS and increased glycolysis deprive the execution machinery of substrate, reducing DLAT activity, suppressing FDX1-dependent lipoylation, and attenuating copper-induced proteotoxicity [7, 75]. The tumor suppressor p53 is a relevant metabolic switch because it antagonizes glycolysis and promotes OXPHOS. Its loss, common in human cancer, therefore both releases cells from canonical apoptotic control and reinforces the glycolytic phenotype that confers cuproptosis resistance [75]. p53 status thus links genomic-integrity control to metabolic death plasticity. This mechanism acts upstream of execution rather than directly neutralizing copper, showing how metabolic state can determine death modality.

A second resistance axis is copper efflux through ATP7A and ATP7B. In response to elevated intracellular copper, these P-type ATPases relocalize from the trans-Golgi network to the plasma membrane or endosomal compartments, exporting copper and preventing the mitochondrial accumulation required for cuproptosis [80, 81]. Cancer cells often upregulate both proteins after copper ionophore treatment, limiting agents such as elesclomol, the most clinically evaluated copper ionophore to date [81, 82]. Genetic or pharmacological ATP7A suppression markedly increases cuproptosis sensitivity and antitumor immunity in breast cancer models, establishing copper export as a therapeutic resistance determinant [81]. The glutathione system

provides an independent chelation mechanism: GSH binds intracellular copper, sequestering it in an inert form and preventing interaction with lipoylated TCA proteins [83]. In pancreatic ductal adenocarcinoma, nuclear factor erythroid 2-like 2 (NFE2L2; also known as NRF2) induces the GSH-biosynthetic enzyme glutamate-cysteine ligase through the SLC25A39 mitochondrial carrier, creating an NRF2-GSH axis that buffers Cu-dependent proteotoxicity [83]. High GSH therefore resists cuproptosis through a mechanism distinct from ferroptosis resistance, although the same antioxidant pool can suppress both modalities by different biochemical routes. This response establishes acquired resistance and can limit ionophore efficacy. GSH chelation is independent of ATPase export and acts before copper reaches lipoylated substrates.

Kinase signaling adds further resistance circuitry. In triple-negative breast cancer (TNBC), copper activates AKT; AKT1-mediated phosphorylation of FDX1 prevents it from supporting protein lipoylation and cuproptosis while reinforcing glycolysis in a self-amplifying loop. This FDX1-AKT axis helps explain high cuproptosis resistance despite elevated copper and supports AKT inhibition as a co-targeting strategy [68]. Liu et al. identified another mechanism in which copper binding to 3-phosphoinositide-dependent protein kinase 1 (PDK1) promotes PDK1-AKT interaction, activates Wnt/β-catenin signaling, and drives cancer stem-cell properties that confer durable resistance. Resistant cells may therefore be enriched for tumor-reinitiating capacity. Under hypoxia, hypoxia-inducible factor 1 alpha (HIF-1α) suppresses mitochondrial respiration, reinforces glycolytic dependence, weakens the OXPHOS context required for cuproptosis, and upregulates copper efflux [84, 85]. Oncogenic signaling, metabolic reprogramming, antioxidant induction, and export thus form a layered, redundant shield that must be understood before cuproptosis can be reliably exploited therapeutically.

Disulfidptosis: cystine metabolism, actin cytoskeleton collapse, NADPH depletion, and cancer cell evasion strategies

Disulfidptosis is a metabolically driven, distinct death process coupling aberrant cystine import to catastrophic cytoskeletal disruption. Liu et al. formally delineated it by showing that cells with high expression of the cystine/glutamate transporter SLC7A11 (also known as xCT) undergo an uncharacterized death under glucose starvation, biochemically and morphologically distinct from apoptosis, necroptosis, or ferroptosis [86]. The finding explains how SLC7A11 overexpression, common across cancer types, can paradoxically create lethal metabolic susceptibility under specific nutrient conditions and expands the plasticity of death programs in malignant tumors. The observation reoriented understanding of how an antioxidant-associated transporter can become a liability. It adds nutrient dependence to death plasticity in malignant tumors.

Disulfidptosis arises from tension between cystine uptake and the capacity to reduce cystine. SLC7A11 constitutively imports extracellular cystine in exchange for glutamate; cytoplasmic conversion to cysteine is a reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent process mediated mainly by thioredoxin and glutaredoxin systems [87]. With adequate glucose, the pentose phosphate pathway (PPP) regenerates enough NADPH. When glucose is limited by deprivation in poorly vascularized tumor regions or pharmacological glucose-transporter inhibition, PPP activity collapses, NADPH falls, and imported cystine cannot be reduced [86, 88]. Cystine and other oxidized disulfides consequently accumulate, shifting redox balance toward hyperoxidation. Rather than causing nonspecific oxidative stress, this produces intermolecular and intramolecular disulfide bonds across F-actin and cytoskeletal proteins, including the Wiskott–Aldrich syndrome protein (WASP)-family verprolin-homologous protein (WAVE) regulatory complex that controls actin polymerization and lamellipodia formation [89]. Clustered regularly interspaced short palindromic repeats (CRISPR)-based screens by Liu et al. showed that WAVE-complex inactivation suppresses disulfidptosis, whereas constitutive activation of Rac1, the small GTPase driving WAVE-dependent actin branching, enhances it. Thus, a cytoskeletal architecture required for motility and integrity becomes the substrate of death under disulfide stress. F-actin networks collapse, the plasma membrane retracts inward, and the cell undergoes rapid structural implosion, unlike apoptotic blebbing or necroptotic organelle swelling [90, 91]. This stress therefore reflects failed reductive capacity rather than simple reactive oxygen species accumulation. Because WAVE and Rac1 have opposing screen effects, actin architecture is a functional determinant of execution.

NADPH depletion acts as both trigger and amplifier of disulfidptosis. As the principal reductant for cytosolic antioxidant systems, NADPH is consumed by cystine import followed by failed reduction, creating a self-reinforcing redox collapse [87, 92]. In SLC7A11-high cells under glucose limitation, the NADPH/$NADP^+$ ratio falls significantly; the extent of depletion determines how far disulfide stress spreads through the cytoskeletal proteome [90]. Yan et al. showed a dose-dependent paradox: moderate SLC7A11 overexpression protects against conventional oxidative stress by sustaining glutathione synthesis, whereas extreme overexpression, as in many aggressive cancers, sensitizes cells to compromised NADPH availability, including exogenous oxidative challenge combined with cysteine loading. SLC7A11 therefore acts as a context-sensitive rheostat, with the adaptation that protects against ferroptosis creating vulnerability to disulfidptosis [7, 93]. Because imported cystine also supplies glutathione, which suppresses ferroptosis, therapeutic exploitation must address these opposing consequences of cystine flux [94].

Cancer cells also co-opt strategies that tolerate or evade disulfide stress. Transcriptional reprogramming modulates NADPH economy: the deubiquitinase BAP1 (BRCA1-associated protein-1), a tumor suppressor, represses SLC7A11, limits cystine import, and maintains elevated NADPH through incompletely characterized mechanisms. High-BAP1 cells have lower NADP+/NADPH ratios and resist glucose starvation-induced disulfidptosis [95]. Thus, loss of a tumor suppressor in cancers such as mesothelioma and clear cell renal carcinoma can paradoxically sensitize cells to this death pathway, whereas BAP1 retention enables evasion. NRF2 likewise activates SLC7A11 under baseline conditions, but tumors can exploit or

overcome this response. In hepatocellular carcinoma (HCC), gaudichaudione H increased disulfidptosis sensitivity by activating the NRF2-SLC7A11 axis under glucose limitation, overcoming cellular buffering [96]. The need for this manipulation suggests intrinsic HCC buffers, likely NRF2-driven induction of PPP enzymes such as glucose-6-phosphate dehydrogenase (G6PD) and malic enzyme, which partially replenish NADPH when glucose is curtailed.

The thioredoxin axis provides another evasion layer. Tang et al. found that thioredoxin reductase 1 (TrxR1) is overexpressed in glioblastoma cells with activated transcriptional coactivator with PDZ-binding motif (TAZ) signaling, buffering disulfide stress during glucose starvation by sustaining thioredoxin-dependent disulfide reduction. TrxR1 inhibition sensitized these cells to disulfidptosis, and disulfide-reducing agents reversed the resulting death, consistent with the execution mechanism described by Liu et al. Tumors with constitutively active Hippo effectors or other drivers of TrxR1 overexpression may therefore shield against cytoskeletal collapse, decoupling SLC7A11-mediated cystine import from lethal downstream effects. Endoplasmic reticulum stress is an additional resistance mechanism: Wang et al. found that glucose-deprived SLC7A11-high cells mount an ER-stress response that partly counteracts disulfide cytotoxicity; pharmacological suppression cooperates with SLC7A11 activity to enhance disulfidptosis, indicating that ER proteostasis buffers disulfide burden beyond cytoskeletal proteins [97]. Wan et al. added an immunological dimension, showing that tumor cells with high SLC7A11 outcompete tumor-infiltrating $CD8^+$ T lymphocytes for extracellular cystine, inducing T-cell exhaustion and ferroptosis while remaining protected from disulfidptosis through adequate glucose metabolism. This sequestration is microenvironmental death evasion: tumors resist their own demise while weaponizing disulfide stress against immune effectors, with implications for immune-checkpoint blockade failure in SLC7A11-high malignancies [98, 99]. These mechanisms extend beyond direct control of cytoskeletal disulfides to redox buffering, proteostasis, and immune competition. Their coexistence may explain variation in disulfidptosis sensitivity across tumor and microenvironmental contexts.

Other non-canonical and emerging modalities: autophagy-dependent death, anoikis, entosis, parthanatos, and lysosomal cell death

The regulated cell death landscape extends beyond pathways emphasized previously. Additional modalities—autophagy-dependent cell death, anoikis, entosis, parthanatos, and lysosomal membrane permeabilization-driven death—suppress malignant growth under physiological conditions but are systematically evaded by established tumors. Although mechanistically heterogeneous and less completely characterized than apoptosis or ferroptosis, they illuminate death plasticity because they interface with matrix adhesion, metabolic stress, lysosomal integrity, and NAD^+ metabolism, all altered by malignant transformation. Their collective importance for defining the full architecture of death plasticity in cancer is substantial. p53, the most universally mutated tumor suppressor, therefore acts not only as a transcriptional activator of apoptotic genes but also as a pleiotropic regulator of autophagy-dependent cell death, entotic cell death, and parthanatos, integrating genotoxic stress across the regulated death network [10].

Autophagy-dependent cell death (ADCD) remains contested because autophagy—the ATG protein-directed sequence of phagophore nucleation, autophagosome maturation, and lysosomal cargo degradation—usually promotes tumor-cell survival under nutrient deprivation, hypoxia, and therapeutic stress [100]. It is primarily cytoprotective and homeostatic rather than an execution pathway. ADCD should therefore be defined by stringent genetics: death must depend on autophagy flux, resist apoptosis or necroptosis inhibition alone, and be abrogated by silencing core components ATG5, ATG7, or Beclin-1 [9, 97]. Autophagy supports cancer-cell survival by mitophagy, which removes damaged mitochondria, limits ROS and MOMP; recycling aggregates and organelles to preserve metabolism during nutrient limitation; and selective degradation of pro-apoptotic proteins, notably p62/SQSTM1-dependent targeting of caspase-8 aggregates [101]. PI3K-AKT-mTOR suppresses autophagy initiation through inhibitory phosphorylation of unc-51-like autophagy activating kinase 1 (ULK1), so the hyperactivated survival network that protects against apoptosis also constrains ADCD [11]. This creates convergent resistance at the level of survival signaling. Beclin-1, the catalytic core of the vacuolar protein sorting 34 (VPS34)/class III phosphatidylinositol 3-kinase (PI3KC3) complex required for autophagosome nucleation, is monoallelically deleted in a substantial proportion of breast and ovarian cancers, initially suggesting tumor suppression through ADCD. However, Beclin-1 loss mainly impairs homeostatic and cargo-selective functions without necessarily abolishing basal autophagy flux, cautioning against inferring autophagy's death-versus-survival role from single-gene alterations [100]. ADCD's actionable relevance is clearest in its convergence with ferroptosis: NCOA4-mediated ferritinophagy releases labile iron, whereas sequestosome 1 (SQSTM1)/p62-directed lipophagy increases PUFA availability. Genetic deletion of either receptor substantially attenuates ferroptotic sensitivity, identifying autophagy as an upstream ferroptotic amplifier and autophagy inhibition as a resistance mechanism against ferroptosis-inducing therapies [102]. These are selective autophagy receptors linking cargo choice to drug response.

Anoikis, from the Greek for homelessness, is apoptotic death triggered by disruption of integrin-extracellular matrix (ECM) interactions. In normal epithelia, these interactions maintain survival through constitutive outside-in signaling via focal adhesion kinase (FAK)-PI3K-AKT and RAS–extracellular signal-regulated kinase (ERK) axes [103]. Because anoikis prevents anchorage-independent survival needed for circulating tumor-cell survival and metastatic colonization, resistance is a key metastatic determinant. The physiological function of this checkpoint is to prevent anchorage-independent survival, and its mechanisms clarify cancer dissemination [24, 104]. Cancer cells acquire resistance through mechanisms intertwined with epithelial-mesenchymal transition (EMT). EMT factors Twist, Snail, Vimentin, and ZEB1 remodel surface integrins, shifting from predominantly

α6β4 laminins, which promote anoikis after ECM withdrawal, toward αvβ3 vitronectin and fibronectin receptors. Soluble ECM fragments in circulation or metastatic sites can ligate the latter and sustain FAK signaling without stable substratum contact [103]. KRAS and PIK3CA mutations constitutively activate survival signals normally extinguished by detachment, whereas EGFR and human epidermal growth factor receptor 2 (HER2) overexpression maintain RAS-ERK and PI3K-AKT flux through autocrine growth-factor loops that substitute for integrin engagement [24]. MCL-1 and BCL-XL are transcriptionally upregulated in resistant cells, countering BIM-dependent apoptosis after integrin withdrawal and linking adhesion to intrinsic apoptosis. These anti-apoptotic proteins directly counter BIM-dependent signaling, making co-targeting these networks rational [104]. Anoikis resistance thus converges EMT, oncogenic signaling, and BCL-2 dysregulation at a nodal vulnerability whose therapeutic exploitation could suppress dissemination, even after primary-site invasion.

Entosis is a non-cell-autonomous death modality in which a viable cell invades and is internalized by another, forming an entotic vacuole; the inner cell may subsequently die through host-cell lysosomal degradation, making the resulting cell-in-cell structure non-autonomous in origin [4, 10]. First described in detached cancer epithelial cells, it differs from phagocytosis, which engulfs an already dead or opsonized cell: the engulfed cell remains viable and actively contracts through RhoA–Rho-associated coiled-coil-containing protein kinase (ROCK) signaling to drive its own internalization [4]. p53 positively regulates entosis in the inner cell; its activation promotes ROCK-dependent contractility and engulfment, whereas p53 loss reduces engulfment; p53 thus acts within the internalized cell, suggesting that some tumor suppression operates through this non-apoptotic route [10]. Entosis is biologically ambivalent. Although entotic death removes some cancer cells, surviving host cells gain volume and nutrients and may proliferate. If lysosomal digestion is incomplete, the inner cell can escape and divide within the host cytoplasm, generating aneuploid progeny through asymmetric division and potentially increasing intratumoral heterogeneity [4, 9]. Thus, entosis may be tumorigenic or tumor-suppressive depending on completion, illustrating why non-canonical death must be assessed in cellular and microenvironmental context rather than by execution frequency alone.

Parthanatos, named for Thanatos and centered on poly ADP-ribose polymerase (PARP), is regulated necrotic death driven by PARP-1 hyperactivation after extensive DNA damage, especially alkylator-, oxidative injury-, or radiation-induced single-strand breaks [10, 104]. Hyperactivation generates long, branched poly-ADP-ribose (PAR) chains, consuming NAD^+ and ATP until energy stores become incompatible with viability. This depletion is a defining energetic feature of the modality. PAR chains directly translocate to mitochondria, releasing apoptosis-inducing factor (AIF), which enters the nucleus and causes large-scale DNA fragmentation without caspase activation—a caspase-independent, necrotic-phenotype route distinct from apoptosis biochemically and morphologically [104, 105]. Parthanatos is particularly relevant in breast cancer susceptibility gene 1 or 2 (BRCA1/2)-deficient and other homologous recombination-defective tumors. PARP inhibitor-induced synthetic lethality, initially conceived as apoptosis induction, is now understood to engage parthanatic execution when lesions are extensive and unresolvable. PARP inhibition therefore titrates the DNA damage-to-PARP activation balance toward parthanatos rather than merely suppressing growth signaling [9]. The outcome depends on extensive, unresolved lesions rather than repair blockade alone. Cancer cells evade this death by overexpressing poly ADP-ribose glycohydrolase (PARG), which removes PAR before it reaches the threshold for mitochondrial AIF release; NAD^+ biosynthetic enzymes, especially nicotinamide phosphoribosyltransferase (NAMPT), which replenish PARP-1-depleted NAD^+ and energy; and AIF-sequestration proteins at the mitochondrial outer membrane [10, 104].

Lysosomal cell death (LCD) is initiated by lysosomal membrane permeabilization (LMP), partial or complete disruption of the lysosomal limiting membrane that releases cathepsins and other hydrolases into the cytoplasm. These enzymes cleave Bid to tBid, activate caspases, or cause caspase-independent death through mitochondrial damage [9]. Cancer-relevant LMP triggers include photodynamic therapy, lysosomotropic hydroxychloroquine, chemotherapeutics such as doxorubicin and siramesine, and ROS-generating conditions, which converge on lysosomal destabilization [9]. These triggers share lysosomal membrane destabilization as their common mechanism denominator. LCD can bypass the BCL-2 family checkpoint governing mitochondrial apoptosis because cathepsin-mediated tBid cleavage follows LMP rather than precedes MOMP. Accordingly, cells with high BCL-2 or BCL-XL expression that resist direct BH3-mimetic therapy may remain LCD-sensitive [97]. Resistance involves heat shock proteins, particularly heat shock protein 70 (HSP70), which stabilizes lysosomal membranes by binding bis(monoacylglycero)phosphate lipids, and transcription factor EB (TFEB)-driven lysosomal biogenesis, which expands a redundant compartment able to buffer focal permeabilization [4, 9] and thereby reduce the impact of localized membrane injury. Integration of lysosomal biology into RCD, the proton sponge mechanism as a pharmacologically exploitable route to LMP, and LCD's convergence with autophagy, parthanatos, and inflammatory signaling establish lysosomal death as therapeutically relevant, although deeper mechanistic characterization is needed for rational clinical deployment [7, 9].

Death pathway crosstalk and cancer death plasticity

Viewing regulated cell death modalities as interconnected nodes rather than isolated linear programs marks a major shift in cancer biology. Each pathway—apoptosis, ferroptosis, pyroptosis, necroptosis, cuproptosis, disulfidptosis, and non-canonical modalities—has a distinct molecular identity, morphology, and metabolic dependence. Mechanistic individuality therefore coexists with molecular promiscuity. Yet shared regulators, upstream sensors, and bidirectional crosstalk mean that activation or suppression of one pathway is rarely without consequence for the others [37]. This network creates cancer death plasticity: malignant cells evade therapy not

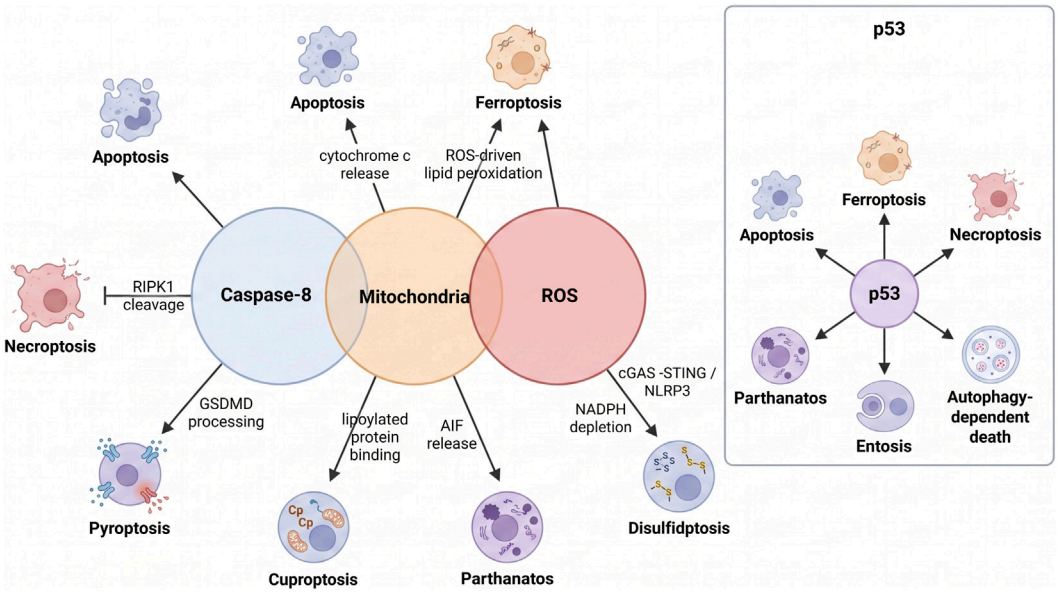


FIGURE 5
Interconnections among regulated cell-death pathways involving caspase-8, mitochondria, ROS, and p53. Caspase-8 suppresses necroptosis by cleaving RIPK1 and is linked to apoptosis through cytochrome *c* release and to pyroptosis through GSDMD processing. Mitochondrial pathways connect to cuproptosis through lipoylated proteins and to parthanatos through AIF release. ROS promotes ferroptosis through lipid peroxidation and is associated with disulfidptosis following NADPH depletion; cGAS–STING and NLRP3 signaling are also indicated. The inset summarizes p53's links to apoptosis, ferroptosis, necroptosis, parthanatos, entosis, and autophagy-dependent cell death. Arrows indicate pathway relationships, while the T-bar denotes inhibition. Abbreviations: AIF, apoptosis-inducing factor; GSDMD, gasdermin D; NADPH, reduced nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species.

by disabling one pathway but by dynamically navigating the network's full topography, redistributing dependence across the regulated death landscape under therapeutic, immunological, and metabolic pressures (Figure 5) [106, 107].

The caspase family demonstrates molecular sharing across death pathways. This versatility makes the caspase family a central crosstalk node. Caspase-8, classically assigned to extrinsic apoptosis, suppresses necroptosis by cleaving and inactivating RIPK1, a direct negative regulator of the RIPK3-MLKL axis. It also participates in PANoptosome assembly, bridging apoptotic and necroptotic modules, and under specific stimulatory conditions processes gasdermin D to contribute to pyroptosis [16, 40]. Thus, caspase-8 status determines sensitivity to three modalities; its transcriptional silencing in melanoma, colorectal cancer, and neuroblastoma produces composite resistance not captured by apoptosis alone [9, 13]. The composite phenotype spans apoptosis, necroptosis, and pyroptosis. Caspase-3 provides a second example: during classical apoptosis it can cleave gasdermin E, converting execution to inflammatory pyroptosis depending on GSDME expression. Cancer-specific GSDME silencing therefore enforces immunological silence on an otherwise immunogenic death [108, 109]. This expression-dependent switch converts apoptosis into inflammatory pyroptosis. Death's immunogenicity or tolerance consequently depends on cellular composition at demise, which cancer cells remodel epigenetically and transcriptionally to limit immune consequences [12].

Mitochondria are a convergence hub for regulated death. They consequently occupy a privileged position in the crosstalk network. Besides cytochrome c release and apoptosome-mediated caspase activation in intrinsic apoptosis, they contribute to ferroptosis through oxidative phosphorylation-derived ROS driving lipid peroxidation; cuproptosis through copper binding to lipoylated TCA cycle proteins in the matrix; disulfidptosis through NADPH depletion after failed cystine reduction; and parthanatos through AIF release after PARP-1 hyperactivation [110]. Mitochondrial membrane potential and matrix redox state therefore jointly modulate susceptibility across these modalities, giving the network metabolic coherence not evident from isolated pathways [74]. These shared variables connect death sensitivity to mitochondrial metabolism. The near-universal Warburg phenotype of cancer—elevated glycolysis with suppressed OXPHOS despite aerobic conditions—attenuates all four: reduced TCA flux limits lipoylation-dependent cuproptosis, reduced mitochondrial ROS dampens ferroptotic lipid peroxidation, and attenuated OXPHOS limits the AIF-releasing capacity that drives parthanatos [7]. The attenuation is global rather than pathway-specific. Warburg metabolism is thus both a biosynthetic adaptation and broad mitochondrial death-resistance strategy, informing therapies that exploit metabolic cell death.

Ferroptosis–autophagy crosstalk shows how one interaction can be pro-death or pro-survival according to context and direction. Ferritinophagy, NCOA4-receptor-mediated selective ferritin degradation, releases labile iron that feeds Fenton chemistry and lipid-radical generation, potentiating ferroptosis. Lipophagy mobilizes lipid droplets to supply free PUFAs for membrane-phospholipid incorporation and peroxidation [102, 109]. Here autophagy amplifies ferroptosis. The two pathways are therefore

functionally synergistic in this configuration. Conversely, it can suppress ferroptosis by removing damaged, peroxidized organelles before lipid-peroxidation signals spread, degrading pro-ferroptotic proteins through chaperone-mediated autophagy, and preserving nutrient-deprived-cell metabolism and GPX4 activity [109]. Cancer cells exploit this duality by modulating autophagic flux while retaining cytoprotection; differential expression and post-translational control of cargo receptors may underlie this selective regulation and add death plasticity at the intersection of these programs. This selective autophagy regulation reflects differential cargo-receptor control. The same crosstalk can therefore either intensify or limit oxidative injury. Ferroptosis and pyroptosis also connect through cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING), activated by oxidatively damaged mitochondrial and nuclear DNA released during lipid peroxidation to drive NLRP3 inflammasome assembly, and through GSDMD N-terminal domain-mediated permeabilization of lipid-peroxidation-primed membranes. This continuum may amplify the immunogenic effects of either pathway [109, 111].

Reactive oxygen species are a shared currency of regulated cell death crosstalk, linking oxidative and inflammatory pathways in a redox continuum whose signaling or lethal polarity depends on concentration, source, and antioxidant capacity [104]. NRF2-KEAP1 illustrates this master logic: NRF2 induces SLC7A11 and GPX4 to suppress ferroptosis, HMOX1 to regulate iron flux, GSH biosynthetic enzymes to limit cuproptosis and disulfidptosis, thioredoxin reductase to buffer oxidative stress, and NQO1 to sustain CoQ10 for FSP1-mediated ferroptosis suppression. One transcriptional program thus antagonizes multiple ROS-dependent deaths [63]. NRF2 activation consequently promotes survival under redox conditions that would otherwise trigger regulated cell death, making KEAP1-mutant cancers resistant across the oxidative death spectrum. The tumor microenvironment adds spatial heterogeneity: cancer-associated fibroblasts secrete paracrine factors and exosome-derived microRNAs that modulate adjacent cancer-cell RCD sensitivity. $CD8^+$ T cell-derived IFN-γ downregulates SLC7A11 through IRF1, sensitizing cancer cells to ferroptosis, whereas cancer cells upregulate competing survival mechanisms and suppress T-cell function through cystine depletion [105, 112]. This ecological competition, in which one currency mediates immune killing and cancer survival, makes death plasticity non-cell-autonomous and demands an ecosystem-level analysis.

p53 distills cross-pathway death regulation into a clinically consequential example. This extends the apoptotic functions detailed above across the death network. In addition to transactivating multiple pro-apoptotic BCL-2 family members and engaging BCL-2 and BCL-XL non-transcriptionally at mitochondrial membranes, wild-type p53 represses SLC7A11 and upregulates SAT1 and ALOX12 to enhance PUFA peroxidation; drives necroptosis through transcriptional upregulation of MLKL; promotes autophagy-dependent cell death through DRAM1 induction; facilitates entosis through RhoA-ROCK-dependent contractility in the internalized cell; and regulates parthanatos through modulation of PARP-1 activity [10]. TP53 mutation in approximately half of all human cancers therefore removes apoptotic surveillance and positive input into no fewer than six additional death programs, creating a broad resistance phenotype underestimated by an apoptosis-only view. This is not simply an academic distinction but a prerequisite for rational combination design. This network perspective is essential for combinations that overcome redundant resistance, convert immunologically cold deaths into immunogenic ones, and exploit metabolic and signaling vulnerabilities created by pathway crosstalk [97, 113].

Cell death in the tumor microenvironment and immunogenic cell death

The tumor microenvironment (TME) is not a passive backdrop for cancer growth and death; it is an active, dynamic, immunologically contested ecosystem whose cellular composition, metabolic state, and inflammatory tone are shaped by how tumor cells die [114]. This view has reframed cancer therapy: the goal is not merely to kill tumor cells, but to kill them while converting an immunologically cold, immune-excluded lesion into a hot, immune-infiltrated lesion sustaining durable adaptive immunity against residual and metastatic disease [12, 115]. Immunogenic cell death (ICD) is a functionally defined regulated cell-death category that stimulates innate and adaptive responses through spatiotemporal control of damage-associated molecular patterns (DAMPs) and pro-inflammatory cytokines [116]. Immunogenic versus tolerogenic death depends not simply on lysis, but on molecular signals displayed by dying cells or released extracellularly and on the context in which they are received, making ICD a nuanced and therapeutically demanding oncology concept (Figure 6).

Canonical ICD hallmarks emerged from studies of immunogenic chemotherapeutics, including anthracyclines, oxaliplatin, and cyclophosphamide, and center on three DAMPs: pre-apoptotic surface exposure of calreticulin (CRT) on the plasma membrane's outer leaflet, an "eat-me" signal for dendritic cells (DCs) and macrophages; active ATP secretion during blebbing, a "find-me" signal that attracts phagocytes and activates the NLRP3 inflammasome; and passive HMGB1 release from the nucleus after membrane permeabilization, engaging Toll-like receptor 4 on DCs to promote antigen presentation and co-stimulatory molecule upregulation [12]. CRT exposure, ATP secretion, and HMGB1 release are surrogate markers, not proof of ICD. The functional gold standard is vaccination–challenge: washed syngeneic tumor cells treated with a candidate inducer are administered without adjuvant to immunocompetent syngeneic mice, challenged 1–2 weeks later with live cells of the same line; reduced tumor incidence or growth demonstrates protective antitumor immunity [117]. Dendritic cells must cross-present tumor antigens on major histocompatibility complex class I (MHC I), with costimulation, to prime antigen-specific naïve $CD8^+$ T cells and drive activation, proliferation, and effector differentiation; *in vitro* coculture with naïve syngeneic T cells supports but cannot replace *in vivo* validation. In the appropriate spatiotemporal sequence and competent antigen-presenting-cell context, these signals can promote antigen uptake and cross-presentation, priming antigen-specific naïve $CD8^+$ cytotoxic T lymphocytes (CTLs), key effectors of durable antitumor

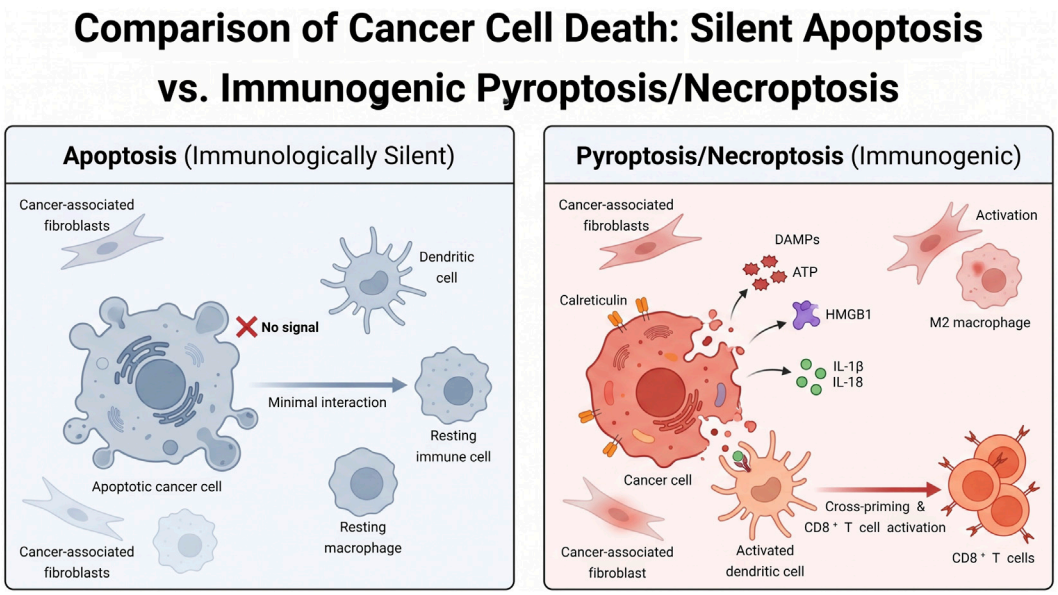


FIGURE 6
Comparison of immunologically silent apoptosis and immunogenic pyroptosis/necroptosis in cancer. Apoptotic cancer cells generally elicit limited immune activation, resulting in minimal interaction with dendritic cells, macrophages, and other immune cells. In contrast, pyroptotic or necroptotic cancer cells expose or release damage-associated molecular patterns (DAMPs), including calreticulin, ATP, HMGB1, IL-1β, and IL-18. These signals promote immune-cell activation, including dendritic-cell activation and cross-priming of $CD8^+$ T cells, thereby facilitating an antitumor immune response. Cancer-associated fibroblasts are shown in both contexts. Abbreviations: DAMPs, damage-associated molecular patterns; HMGB1, high-mobility group box 1; IL, interleukin.

immunity. Endoplasmic reticulum (ER) stress acts upstream of CRT exposure: it activates the protein kinase R-like endoplasmic reticulum kinase (PERK)–eukaryotic initiation factor 2 alpha (eIF2α) arm of the unfolded protein response, driving CRT from its luminal retention site to the plasma membrane through soluble N-ethylmaleimide-sensitive factor (NSF) attachment protein receptor (SNARE)-mediated vesicle fusion, a pathway sensitive to protein disulfide isomerase inhibition. This explains the disproportionate ICD potency of ER-targeting drugs and the emergence of ER-targeted nanomaterials as effective ICD platforms [118, 119]. A parallel mechanism is cGAS-STING activation by cytoplasmic double-stranded DNA from damaged mitochondria or genotoxic-stress-generated micronuclei, inducing type I interferon, DC activation, and CTL recruitment independently of canonical DAMP signaling; STING agonist delivery with cell-death inducers incorporates this pathway into next-generation ICD platforms [120].

ICD biology also depends on the immunogenic potential of each regulated cell-death modality, which varies greatly and is not predictable from lytic versus non-lytic character alone [4, 9]. Necroptosis releases MLKL-dependent contents, including nuclear antigens, cytokines, and mitochondrial DAMPs, while RIPK3 activation recruits neutrophils through C-X-C motif chemokine ligand 1 (CXCL1)- and C-X-C motif chemokine ligand 2 (CXCL2)-dependent signaling, enabling subsequent DC activation. Meier et al. showed that necroptosis optimizes antigen provision by releasing antigens in a temporally extended, plasma membrane-associated manner rather than through rapid bulk necrotic release [13]. It may be the most efficient single-agent ICD modality for adaptive immune priming. Mannion et al.'s RIPK1-specific PROTAC degraders showed that targeted enhancement of necroptotic signaling through RIPK1 degradation produces potent antitumor activity specifically by augmenting ICD, validating necroptosis as a pharmacologically actionable mechanism [121]. Pyroptosis likewise produces a potent signal through gasdermin pore-mediated IL-1β and IL-18 secretion and nuclear and cytoplasmic alarmin release. Yet IL-1β can act on tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) to reinforce immunosuppression rather than CTL activation, making pyroptosis's TME effects context dependent [108, 122]. Pyroptosis-based ICD is thus most effectively translated into antitumor immunity when paired with reprogramming or depletion of suppressive myeloid cells, as in nanomaterials co-delivering pyroptosis inducers with indoleamine 2,3-dioxygenase (IDO) inhibitors or Toll-like receptor (TLR) agonists for synchronized tumor killing and TME remodeling [118].

Ferroptosis may be immunogenic or immunosuppressive depending on tumor context and death stage, and its ability to elicit protective adaptive immunity remains controversial [52, 123]. Reports that ferroptotic cancer cells release oxidized lipid fragments, HMGB1, and ferritin-derived iron, activating DCs and natural killer (NK) cell activity, do not establish functional ICD. In an inducible model, Wiernicki et al. found that early ferroptotic cells impaired DC maturation, were poorly engulfed, and reduced antigen cross-presentation; DCs loaded with these cells failed to protect in a prophylactic vaccination assay, while mixing them with immunogenic apoptotic cells reduced vaccine protection [124]. Conversely, IFN-γ from activated $CD8^+$ T cells promotes cancer-cell ferroptosis by downregulating SLC7A11 through IRF1 and

IRF8, creating a positive adaptive-immunity–ferroptosis feedback loop and rationale for combining ferroptosis inducers with immune checkpoint blockade [125]. Ferroptosis generates oxidized phospholipids, notably oxidized phosphatidylethanolamines, that activate peroxisome proliferator-activated receptor gamma (PPARγ) in macrophages and promote an immunosuppressive M2-like phenotype. Its lipid peroxide-rich TME can impair T cells by driving T-cell ferroptosis through programmed cell death protein 1 (PD-1)-mediated suppression of phospholipid phosphatase 1, as shown by Ping et al. These divergent, context- and stage-dependent effects mean ferroptosis cannot be assumed immunogenic *in vivo* without characterizing TME context, tumor type, and ferroptotic intensity; immunotherapy strategies must protect tumor-infiltrating lymphocytes from bystander ferroptotic stress [123, 126]. Cuproptosis is intrinsically immunogenic: execution-defining proteotoxic stress and mitochondrial damage generate CRT surface exposure, HMGB1 release, and ATP secretion at levels comparable to anthracycline-induced ICD, while cGAS-STING activation has been documented in multiple tumor models [84]. Elesclomol-loaded copper oxide nanoplatforms triggered cuproptosis in melanoma cells, promoted DC maturation, and reshaped the immunosuppressive TME through DAMP release and enhanced major histocompatibility complex class I (MHC I) antigen presentation, providing proof-of-concept for cuproptosis-based ICD as a combined cytotoxic and immune-activating strategy [127].

Beyond dying cells' direct immunogenicity, the TME shapes RCD sensitivity through non-cell-autonomous mechanisms forming distinct layers of immunological resistance to cell death [105]. T cell exhaustion—the progressive loss of effector function in chronically stimulated tumor-infiltrating lymphocytes (TILs)—is driven by TME cytokines, including transforming growth factor beta (TGF-β), interleukin-10 (IL-10), and prostaglandin E2 from TAMs, MDSCs, cancer-associated fibroblasts, and tumor endothelial cells, and maintained by inhibitory receptors on T cells: PD-1, T-cell immunoglobulin and mucin-domain containing 3 (TIM-3), lymphocyte activation gene 3 (LAG-3), and T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) [128]. Exhausted T cells cannot secrete the IFN-γ needed to downregulate SLC7A11 and drive cancer-cell ferroptosis, severing the adaptive immunity–ferroptosis loop and explaining why PD-1 blockade synergizes with ferroptosis inducers: restoring IFN-γ reinstates ferroptotic sensitivity in cancer cells insulated by high SLC7A11 [125, 129]. Cancer cells transfer mitochondria containing mutant mitochondrial DNA (mtDNA) to TILs; these mitochondria resist mitophagy, impair T-cell oxidative metabolism, and reduce killing capacity, revealing immune evasion through organelle transfer rather than cytokine signaling and positioning mitochondrial biology as an unexpected TME-immunology frontier. Chemotherapy-generated senescent cancer cells upregulate programmed death-ligand 2 (PD-L2), not programmed death-ligand 1 (PD-L1), as their primary checkpoint, enabling evasion resistant to standard anti-PD-1 but sensitive to anti-PD-L2 blockade. Thus, chemotherapy-induced death responses can generate immunosuppressive adaptations that limit cytotoxic-treatment benefits [130]. Cancer-cell-death outcome reflects the ecological transaction among dying cells, their signals, and TME capacity to translate them into durable antitumor immunity—an interaction continually disrupted by cancer plasticity and re-engaged by effective immunotherapy [131].

Cancer evasion strategies across death modalities and therapeutic targeting of regulated cell death

Previous sections have shown how cancer cells neutralize the cytotoxic potential of each regulated cell death pathway. This pathway-by-pathway analysis reveals not isolated resistance stories but a coordinated system of death insulation spanning the regulated death network. The unifying principles are master regulatory axes through which single alterations disable multiple pathways, epigenetic and adaptive mechanisms that acquire resistance on therapeutic timescales, and therapeutic strategies that exploit network logic to circumvent layered defenses [97, 106, 107]. What emerges is a deeply structured, simultaneous, and coordinated pattern of resistance, not merely a series of pathway-specific failures.

Master transcription factors and oncogenic signaling nodes form the most consequential cross-pathway resistance architecture because they regulate vulnerability across multiple death programs. PI3K-AKT-mTOR exemplifies this logic. Beyond suppressing apoptosis through BAD phosphorylation, MDM2 stabilization, and IAP induction, constitutive AKT stabilizes SLC7A11 and drives SREBP1-dependent lipogenic reprogramming against ferroptosis, phosphorylates FDX1 to suppress cuproptosis in triple-negative breast cancer, activates mTORC1 to inhibit autophagic flux and ferritinophagy-dependent ferroptosis, and sustains glycolysis, the primary metabolic resistance to cuproptosis and disulfidptosis [11, 63, 68]. These activities establish a single signaling node that couples apoptotic, oxidative, proteotoxic, and metabolic resistance.

Thus, a single gain-of-function PIK3CA mutation or PTEN deletion can confer multi-pathway death resistance that no single-modality therapy can overcome. Wnt/β-catenin hyperactivation follows similar convergent logic: it sustains GPX4 to suppress ferroptosis, upregulates BCL-2 and survivin to suppress apoptosis, and reinforces cancer stem cell identity, which itself resists multiple death modalities through DGAT-mediated lipid droplets and aldehyde dehydrogenase-dependent redox buffering [132, 133]. In cancers with constitutive inflammatory signaling, NF-κB drives the entire anti-apoptotic IAP cluster, induces pro-survival autophagy, and upregulates PD-L1 to evade immune surveillance, linking death-pathway evasion to immune-checkpoint biology (Figure 7) [114, 134].

Epigenetic plasticity is a second unifying mechanism of death resistance. Unlike mutations, it enables cancer cells to switch resistance states on therapeutic timescales and reverse them after selective pressure is withdrawn [9, 111]. Promoter methylation silences GSDME in cancer cells, uncoupling caspase-3 activation from pyroptotic inflammation; DNA methyltransferase or histone deacetylase inhibitors can reverse this silencing and restore pyroptotic immunogenicity in otherwise unresponsive tumors [9, 108]. H3K27me3-mediated repression of RIPK3 in colorectal and

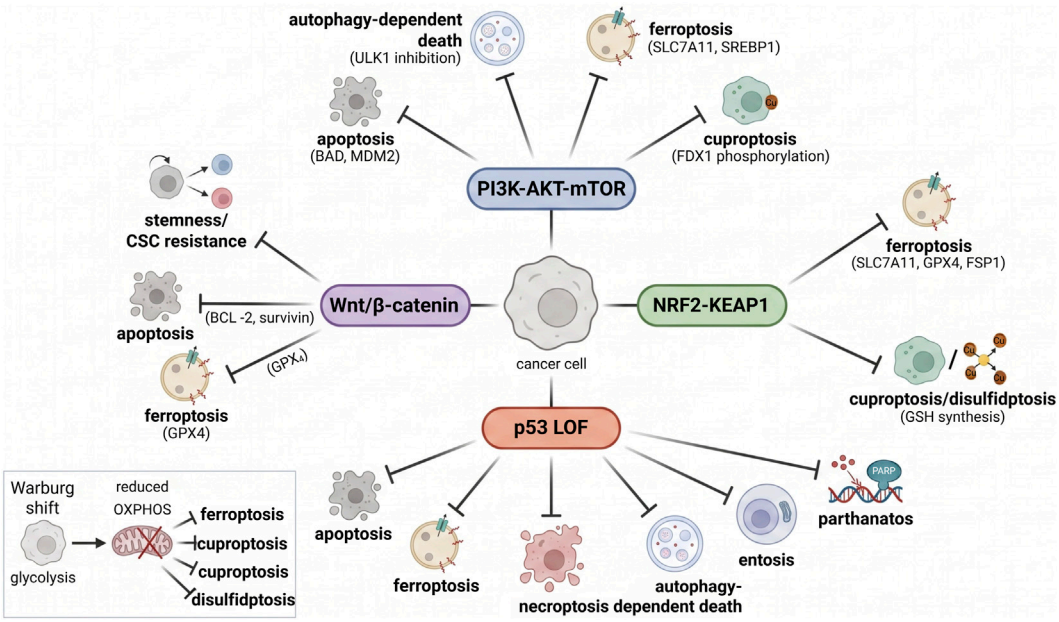


FIGURE 7
Oncogenic signaling and tumor-suppressor loss shape cancer-cell death susceptibility. The schematic summarizes how PI3K–AKT–mTOR, Wnt/β-catenin, and NRF2–KEAP1 signaling, together with p53 loss of function (LOF), are associated with altered susceptibility to regulated cell-death pathways. The pathways are linked to modulation of apoptosis, autophagy-dependent cell death, ferroptosis, cuproptosis, disulfidptosis, necroptosis, entosis, and parthanatos, as well as cancer stemness and cancer stem cell (CSC) resistance. The inset illustrates the Warburg shift from oxidative phosphorylation (OXPHOS) toward glycolysis and its connections to cell-death susceptibility. T-bars indicate inhibitory relationships. Abbreviations: GSH, glutathione; GPX4, glutathione peroxidase 4; LOF, loss of function; OXPHOS, oxidative phosphorylation.

pancreatic cancers silences necroptotic execution and is reversible with EZH2 inhibition, whereas lncRNA-directed heterochromatin formation suppresses FDX1 and DLAT in hepatocellular carcinoma, reducing cuproptotic susceptibility [97, 135]. Non-coding RNAs also regulate death sensitivity post-transcriptionally: miRNA and lncRNA species targeting GPX4, SLC7A11, ACSL4, and RIPK3 are differentially expressed in drug-resistant cells and contribute to resistance acquired after ferroptosis-inducing therapy [9, 136]. Cellular adaptation to targeted therapy follows a resistance continuum marked by progressive epigenetic remodeling rather than sudden mutational switching, indicating that death resistance is a graded, potentially interceptable trajectory rather than a binary transition [107]. This reversibility gives epigenetic resistance distinctive therapeutic implications. Together, these mechanisms create a flexible regulatory layer selected during treatment.

Cancer stem cells (CSCs) and cell-state plasticity constitute a third resistance principle that overlaps with, but is not reducible to, epigenetic regulation. CSCs are hierarchically positioned within tumors, resist conventional therapies, can re-initiate tumors, and occupy niches that sustain immunosuppressive signaling [132]. They show high BCL-2 and MCL-1, constitutive NRF2 activity supporting antioxidant defenses across ferroptosis, cuproptosis, and disulfidptosis, elevated aldehyde dehydrogenase activity that buffers lipid peroxidation, and predominantly glycolytic metabolism that attenuates mitochondria-dependent death [132, 137]. In lung cancer, targeting carnitine palmitoyltransferase 1A (CPT1A), the rate-limiting enzyme in mitochondrial long-chain fatty acid oxidation, overcame CSC-mediated ferroptosis resistance by increasing membrane PUFA and depleting antioxidant capacity sustained by fatty acid oxidation-derived NADPH; it synergized with anti-PD-1 therapy and provided proof of principle for metabolic reprogramming specifically in CSCs [137]. Targeting CSC niches maintained by MDSCs, M2-polarized TAMs, cancer-associated fibroblasts, and regulatory T cells removes paracrine survival signals, reactivates effector immunity, and amplifies ICD-mediated tumor clearance [99, 132]. These properties help explain why CSCs can survive therapies that eliminate more differentiated tumor cells.

These insights have informed combinatorial and network-level therapies that exploit the logic of death resistance rather than target one pathway. The most clinically mature strategy combines BH3-mimetic apoptosis induction with checkpoint blockade: venetoclax plus azacitidine showed that MOMP-driven apoptosis, although immunologically silent alone, can generate sufficient immunogenic priming when checkpoint inhibition is added, producing durable remissions in acute myeloid leukemia (AML) that neither agent achieves alone [14]. Ferroptosis inducers combined with anti-PD-1 or anti-PD-L1 are supported by the finding that IFN-γ from checkpoint-released T cells downregulates SLC7A11 and sensitizes cancer cells to ferroptosis, while ferroptosis-released oxidized lipids amplify DC activation and T cell priming; death induction and immunotherapy therefore reinforce one another bidirectionally [125, 138]. Mitochondria-targeted photodynamic therapy triggering GSDME-mediated pyroptosis converted microsatellite-stable colorectal cancers, canonically unresponsive to PD-1 blockade, into immunotherapy-sensitive lesions in preclinical models, supporting pyroptosis–checkpoint combinations in

immunologically cold tumors [111]. Nanomedicine platforms can co-deliver mechanistically distinct payloads, orchestrate their spatial and temporal release at tumors, and modulate the immunosuppressive TME with TLR agonists, IDO inhibitors, or immune cell-targeting ligands [139]. Machine learning integration of multi-pathway RCD signatures with transcriptomic and clinical data showed that composite indices incorporating apoptotic, ferroptotic, pyroptotic, and cuproptotic expression outperform single-pathway biomarkers for predicting immunotherapy response and prognosis in lung adenocarcinoma [140]. Together, these advances shift the field from potent pathway-specific agents toward complementary, immunologically informed combinations that leverage the full death network against cancer's adaptive resistance machinery. Because nanomedicine can control payload composition and release timing, it is particularly suited to combining death induction with TME remodeling. Composite indices thereby assess network-level death competence rather than a single marker and may capture the redundancy that governs response.

Challenges and future directions

Regulated cell death biology has reached exceptional mechanistic richness and therapeutic opportunity. More than a dozen death modalities, molecular executors characterized at atomic resolution, and cancer-specific evasion mechanisms have transformed cell death from a binary survival question into a granular, actionable oncology frontier. Yet mechanistic understanding has outpaced clinical impact. With the partial exception of BH3-mimetic-induced apoptosis in hematological malignancies, no agent exploiting the non-apoptotic regulated death landscape has achieved regulatory approval for a cancer indication, and mechanistic sophistication has not produced equivalent durable patient benefit [138]. Explaining and bridging this gap is the field's most pressing challenge.

The first challenge is context dependency: sensitivity to a death modality is not fixed by malignant genotype but is a dynamic, state-dependent, microenvironmentally contingent phenotype that changes on therapeutic timescales [106, 107]. França et al.'s resistance-continuum framework showed that therapeutic pressure produces graded epigenetic and transcriptional transitions rather than sudden mutational switches, with resistance states probabilistically accessible from multiple starting cell states. Thus, an agent inducing ferroptosis or cuproptosis in a pretreatment sample may encounter a remodeled sensitivity landscape after one treatment cycle, as near-lethal oxidative or proteotoxic stress rapidly retunes NRF2 targets, SLC7A11 expression, and ATP7A/B copper-efflux activity. Overcoming this dependence on context requires longitudinal, serial monitoring of death-pathway competence during treatment, including single-cell resolution across spatially heterogeneous tumors [140]. Composite RCD signatures integrating multiple pathway components also require prospective clinical cohorts correlating multi-pathway competence with response; no non-apoptotic modality has yet been studied systematically in this design [140]. Monitoring therefore cannot be confined to baseline: treatment itself changes the relevant molecular states. Such signatures can support precision treatment only if validated prospectively in cohorts designed for this purpose.

The second challenge is the lack of validated pharmacological probes for most non-apoptotic pathways, limiting rigorous *in vivo* mechanism-of-action studies. Ferroptosis has well-characterized tools—erastin and sorafenib as System Xc^- inhibitors and RSL3 and ML210 as GPX4 inhibitors—but their pharmacokinetic liabilities, off-target effects, and limited selectivity complicate animal studies and preclude direct clinical development of first-generation inducers [52, 138]. The copper ionophore elesclomol, the most clinically advanced cuproptosis-promoting agent, was developed and tested before its mechanism was known; existing trials therefore lacked biomarker stratification and pharmacodynamic endpoints required by a mechanism-informed program. Retrospective analyses link response to FDX1 expression and OXPHOS status, but prospective validation in dedicated trials remains incomplete [72, 82]. No agent has been approved or entered trials with disulfidptosis induction as its primary mechanism. Its dependence on high SLC7A11 expression plus glucose deprivation—difficult to impose uniformly in vivo—requires delivery strategies that create focal tumor glucose deprivation without systemic hypoglycemia [86]. Addressing these deficiencies requires sustained chemical-biology investment in optimized inducers for each non-apoptotic pathway, paired from the outset with pharmacodynamic biomarkers demonstrating on-target action in clinical specimens. These limitations mean that apparent pathway activation may reflect off-target toxicity rather than the intended death mechanism, complicating comparisons across models and biomarker-guided translation.

Third, the immunological consequences of non-apoptotic death in human tumors remain incompletely characterized and sometimes contradictory, clouding the clinical promise of ICD combinations. Ferroptosis can be immunogenic or immunosuppressive depending on lipid-peroxide concentrations, macrophage polarization, and tumor-infiltrating T-cell function, illustrating that immune output is emergent from interactions among the dying cell, its molecular releases, and TME competence rather than intrinsic to the death modality [123, 141]. Translating ICD potency shown in immunologically intact syngeneic mice using one cell line and treatment into heterogeneous, immunologically complex, pretreated human cancer requires TME characterization and patient stratification absent from most current trials. Moreover, PD-1 signaling directly promotes ferroptosis in tumor-infiltrating $CD8^+$ T cells by suppressing phospholipid phosphatase 1 [129]; checkpoint blockade therefore releases CTL effector function while protecting CTLs from ferroptotic bystander death. This illustrates the unanticipated interactions between death and checkpoint biology in human tumors. Trials exploiting them will need co-primary endpoints for cytotoxic and immune mechanisms, mandatory paired biopsies measuring death-pathway activity and immune composition, and adaptive statistics to identify tumor and patient subgroups most likely to benefit [40, 115].

Fourth, metabolic heterogeneity in solid tumors creates differential death sensitivity among subpopulations in one lesion. Because ferroptosis, cuproptosis, and disulfidptosis are metabolic modalities gated by OXPHOS, NADPH availability, and the labile metal pool, variation among central hypoxic cores, peripheral

proliferative fronts, and stromal interfaces should differentially activate them even under a uniform stimulus [83]. Agents may therefore kill OXPHOS-active cells while sparing glycolytic or hypoxic populations, selecting metabolically resistant, stem-like cells with each cycle. One solution is to convert glycolytic cells to OXPHOS dependence before induction, as shown by PROTAC-based disruption of glycolytic signaling combined with cuproptosis [77]; another is to add pyroptosis or necroptosis, whose execution does not depend on mitochondrial metabolism and can target spared glycolytic cells. Sequential or synchronized multimodality induction, in which one stimulus remodels metabolism and sensitizes cells to another death modality, is promising but experimentally immature. Translation requires understanding inter-pathway metabolic crosstalk, which is only beginning to emerge [7, 109].

Fifth, the field needs standardized, clinically applicable measures of regulated cell death in human tissue. Current pathway-specific assays—C11-BODIPY (a C11-conjugated boron-dipyrromethene fluorescent probe) imaging of lipid peroxidation for ferroptosis, DLAT aggregation staining for cuproptosis, actin-collapse visualization for disulfidptosis, and lactate dehydrogenase (LDH) release or gasdermin-cleavage immunohistochemistry for pyroptosis—were developed for *in vitro* or preclinical use and lack validation as quantitative clinical biomarkers [72, 86]. Multiplexed, formalin-fixed paraffin-embedded tissue-compatible immunohistochemical or transcriptomic assays scoring several death activities in one biopsy would enable mechanism-of-death attribution in treated tumors, currently impossible. Liquid biopsies detecting circulating DAMPs, cell-free oxidized lipids, or death-specific protein fragments could provide noninvasive pharmacodynamic monitoring, especially of ICD dynamics and immune-activation kinetics during combination therapy [12, 140]. Machine-learning integration of multi-pathway competence with tumor transcriptomics, epigenomics, metabolomics, and outcomes in large retrospective cohorts offers a near-term route to predictive biomarker combinations for prospective trial stratification [140].

Several emerging directions may generate major conceptual advances in the next decade. The identification of lysozincrosis, a zinc-dependent metabolic death, and alkaliptosis, a pH-dependent death triggered by aberrant intracellular alkalization, suggests that the cancer-relevant catalogue is incomplete; systematic studies of other metal ions, pH perturbations, and metabolic stresses will expand the death network [7]. Cancer cells' transfer of mitochondria bearing mutant mtDNA to tumor-infiltrating lymphocytes, impairing T-cell function, opens a dimension of death plasticity in which mitochondrial dysfunction actively disables immune killers rather than merely resisting death. PROTAC-based degradation of resistance nodes—RIPK1-directed PROTACs enhancing necroptotic ICD [121] and AKT-directed degradation resensitizing cuproptosis-resistant TNBC [68]—may remove resistance proteins more completely than conventional kinase inhibition and thereby overcome incomplete target suppression. Integrating single-cell multi-omics, spatial transcriptomics, and live-cell death reporters in intact human tumor tissue should resolve death competence across cell states, reveal which subpopulations execute which modalities under which conditions, and provide the cell-type-resolved maps needed for rational combinations [107]. The field is therefore molecularly sophisticated and therapeutically promising; it now needs biomarker platforms, trial designs, combination strategies, and mechanistic monitoring capable of converting that sophistication into durable survival benefit.

Conclusion

Cancer's regulated cell death landscape has expanded from an apoptosis-centric narrative into an interconnected network of distinct but functionally convergent modalities, each with a defined therapeutic entry point and cancer-specific evasion architecture. The central obstacle to durable benefit is not a lack of lethal pathways but their coordinated suppression through master hubs—PI3K-AKT-mTOR, NRF2-KEAP1, p53, and Wnt/β-catenin—reinforced by the Warburg phenotype, which functions as a death-resistance strategy rather than mere biosynthetic convenience. Viewing death plasticity as an organizing principle shifts therapy from ever more potent single-pathway inducers toward combinations that collapse network redundancy, convert immunologically silent deaths into immunogenic ones, and exploit the metabolic and signaling dependencies required for survival. Translation still requires validated probes for non-apoptotic pathways, standardized tissue- and liquid-biopsy biomarkers of multi-pathway competence, and trials capturing context-dependent sensitivity as tumors evolve under pressure. The field has supplied the conceptual and molecular vocabulary; it must now build the clinical infrastructure that converts cancer-death plasticity into durable patient survival.

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(Grammarly Inc.) in order to improve the English language, grammar, and readability of the manuscript. All scientific content, conceptual framework, literature synthesis, and intellectual contributions are entirely the work of the authors. The authors have reviewed and take full responsibility for the content of this publication.

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