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Review

Regulated Cell Death and Cancer Drug Resistance: From Molecular Mechanisms to Clinical Translations

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Abstract

Cancer drug resistance remains a profound and multifaceted obstacle to the success of contemporary therapeutic regimens, substantially contributing to poor clinical outcomes and reduced patient survival. A central mechanism underlying this challenge is the remarkable ability of malignant cells to evade programmed and regulated cell death (RCD) pathways, thereby promoting cellular persistence, increased adaptability, increased aggressiveness, and metastatic dissemination. This comprehensive review highlights current knowledge on the canonical intrinsic and extrinsic apoptotic pathways, while other RCD modalities, including necroptosis, ferroptosis, pyroptosis, autophagy-dependent cell death, and cuproptosis, as well as alternative pathways, such as parthanatos, entosis, NETosis, lysosome-dependent cell death (LCD), alkaliptosis, and oxeiptosis, are thoroughly integrated. Emphasis is placed on the intricate molecular regulatory networks governing these death pathways and their dynamic crosstalk within the complex tumor microenvironment (TME). We provide an in-depth examination of pivotal signaling cascades, including those mediated by the BCL2 family, caspases, mitogen-activated protein kinase (MAPK), and JAK-STAT pathways, which collectively orchestrate the delicate equilibrium between cell survival and death. Furthermore, our review critically evaluates how cancer-associated factors, including epithelial-mesenchymal transition (EMT), multidrug resistance (MDR) via efflux transporters, and the immunomodulatory influence of the TME, converge to exacerbate therapeutic refractoriness. By integrating cutting-edge molecular insights with translational evidence, this review delineates promising therapeutic strategies that exploit RCD vulnerabilities to restore cell death sensitivity and dismantle resistance mechanisms, thereby catalyzing the advancement of precision oncology approaches grounded in mechanistic rigor and clinical relevance.

Keywords: regulated cell death (RCD), drug resistance, neoplasms, apoptosis, nonapoptotic cell death, tumor microenvironment, precision oncology

INTRODUCTION

Therapeutic resistance remains one of the most formidable challenges in modern oncology, substantially limiting the long-term efficacy of anticancer treatments [1, 2]. Although many malignancies initially respond to therapeutic interventions, tumor cells frequently acquire adaptive mechanisms that enable survival under therapeutic pressure, ultimately leading to disease recurrence, progression, and treatment failure [3, 4]. Despite remarkable advances in precision medicine and

targeted therapies, resistance continues to represent a major clinical obstacle and is often associated with increased tumor aggressiveness and poor patient outcomes. Conventional treatment modalities, including surgery, chemotherapy, and radiotherapy, are similarly hindered by the remarkable plasticity of cancer cells, particularly cancer stem cells (CSCs), which contribute to tumor dormancy, relapse, and therapeutic resistance [5, 6]. Consequently, considerable efforts have been directed toward developing more effective therapeutic strategies, including novel chemotherapeutic agents, optimized treatment schedules, and drug repurposing methods designed to overcome resistance and improve clinical outcomes [7, 8]. Nevertheless, a comprehensive understanding of the molecular mechanisms underlying both intrinsic and acquired resistance remains an urgent unmet need in cancer therapy [9-11].

A fundamental determinant of tumor development and the therapeutic response is the balance between cellular proliferation and regulated cell death (RCD). Under physiological conditions, tightly controlled cell death programs maintain tissue homeostasis by eliminating damaged, aged, or potentially malignant cells [12]. Cancer disrupts this balance by promoting uncontrolled proliferation while simultaneously suppressing cell death pathways, thereby enabling malignant transformation and tumor progression [13]. Apoptosis, the most extensively characterized form of RCD, serves as a critical tumor-suppressive mechanism; however, cancer cells frequently acquire genetic and epigenetic alterations that disable apoptotic signaling and confer a survival advantage [14, 15]. Increasing evidence indicates that the ability to evade multiple forms of cell death represents a hallmark of cancer and contributes substantially to therapeutic resistance [16, 17].

In addition to its direct effects on tumor cell survival, RCD has emerged as a key regulator of the tumor microenvironment (TME) [18]. Recent advances have identified several nonapoptotic forms of RCD, including necroptosis, ferroptosis, pyroptosis, and autophagy-dependent cell death, each of which exerts distinct effects on both cancer cells and the surrounding stromal and immune compartments. These pathways not only influence tumor growth and therapeutic responsiveness but also actively shape the inflammatory and immunological landscape of tumors [19]. For example, nonapoptotic RCDs, such as necroptosis, are frequently accompanied by the release of danger/damage-associated molecular patterns (DAMPs) and proinflammatory mediators that can stimulate antitumor immunity, whereas chronic activation of inflammatory signaling may paradoxically promote tumor progression, immune evasion, and treatment resistance [20-22]. Similarly, ferroptosis has attracted considerable attention because of its ability to eliminate apoptosis-resistant cancer cells while simultaneously influencing immune cell function and metabolic interactions within the TME [23].

The dual role of RCD in regulating both tumor cell fate and the TME has profound implications for cancer therapy. By directly eliminating malignant cells and indirectly modulating immune surveillance, inflammation, stromal interactions, and therapeutic sensitivity, RCD pathways represent attractive targets for next-generation anticancer strategies [24, 25]. A growing body of experimental and clinical evidence has demonstrated that manipulation of these pathways can increase treatment efficacy, overcome resistance in refractory tumors, and potentially improve patient outcomes. Furthermore, the molecular components of RCD pathways are increasingly being explored as predictive biomarkers and therapeutic targets for personalized cancer treatment.

In the current review, we comprehensively discuss the diverse forms of RCD and their multifaceted roles in cancer biology. Particular emphasis is placed on the dual impact of RCD on tumor progression through the regulation of cancer cell survival and through remodeling of the tumor microenvironment, including immune and inflammatory responses. We also discuss the translational potential of targeting RCD pathways as innovative therapeutic approaches for overcoming resistance and improving the effectiveness of anticancer therapies.

ORIGINS AND MOLECULAR UNDERPINNINGS OF REGULATED CELL DEATH

RCD encompasses a group of genetically controlled cellular processes that are essential for maintaining tissue homeostasis, development, and organismal health. Since the introduction of the concept of apoptosis by John Kerr, Andrew Wyllie, and Alastair Currie in 1972 [26] (**Figure 1**), extensive research has revealed that RCD comprises multiple distinct modalities beyond apoptosis, including necroptosis, pyroptosis, ferroptosis, entotic cell death, netotic cell death, parthanatos, lysosome-dependent cell death, autophagy-dependent cell death, alkaliptosis, and oxeiptosis [27]. Dysregulation of these pathways contributes to the development and progression of numerous diseases, particularly cancer [12].

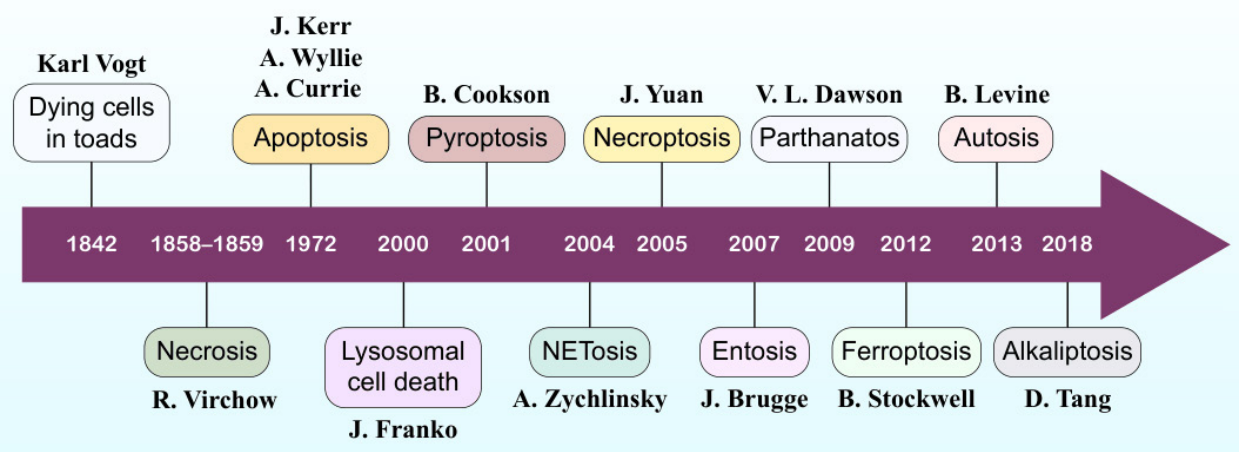


Figure 1. Timeline of the discovery and conceptualization of regulated cell death modalities. The timeline depicts the historical progression of major forms of cell death from 1842-2018, which are aligned on a horizontal timeline and annotated with the researchers who first described or named each process.

In tumors, RCD plays a dual role; on the one hand, the activation of cell death pathways suppresses tumor initiation and growth by eliminating damaged or transformed cells, while on the other hand, alterations in RCD signaling can promote tumor survival, progression, immune evasion, and therapeutic failure [19]. Given the increasing recognition of the complex interactions between RCD and cancer, understanding the molecular characteristics of individual RCD pathways has become increasingly important. The following sections provide an overview of the major nonapoptotic RCD mechanisms and their relevance to cancer biology. **Table 1** summarizes the key RCD modalities and their reported roles in cancer.

Apoptosis

Apoptosis is a precisely orchestrated biological process essential for maintaining tissue equilibrium in multicellular systems, facilitating the orderly elimination of superfluous or compromised cells [28]. This mechanism operates through multiple signaling cascades, which are primarily divided into two principal categories: the mitochondrial (intrinsic) route and the death receptor (extrinsic) route. A comprehensive understanding of these apoptotic systems is foundational for elucidating disease pathogenesis arising from their dysfunction and, subsequently, for creating targeted interventions addressing specific apoptotic mechanisms or genetic elements [29].

The mitochondrially mediated intrinsic apoptotic route functions under stringent regulation, responding to various cellular stressors through the liberation of death-promoting factors (see **Figure 2** for more details). Maintaining mitochondrial structural integrity and determining cellular destiny depends critically on the precise quantitative equilibrium between death-promoting and death-inhibiting constituents of the BCL2 protein family. This mechanism culminates in cellular dismantling, producing apoptotic fragments with surface alterations that enable their rapid recognition and clearance by phagocytic cells [30, 31].

The extrinsic apoptotic pathway begins when extracellular death ligands, such as TNF and FASLG (Fas ligands), bind to specific cell-surface death receptors, including TNFRSF1A/TNFR1 and FAS/CD95 [32-34]. Ligand binding induces receptor trimerization, enabling the recruitment of adaptor proteins such as TRADD through death domain interactions [35-37]. These adaptors facilitate the assembly of the death-inducing signaling complex (DISC), which recruits and activates the initiator CASP8, initiating the downstream apoptotic cascade [38-41]. This signaling process is crucial for immune regulation, homeostasis, and removal of damaged or infected cells.

In addition to the established intrinsic and extrinsic routes, less characterized caspase activation mechanisms exist, including the participation of CASP12 and CASP2, enzymes involved in ER stress-triggered apoptosis. CASP12 (in rodents) and human CASP4 predominantly facilitate apoptosis in response to ER stress, which occurs when improperly folded or unfolded proteins accumulate, activating the unfolded protein response/UPR. This cascade can also stimulate the release of proinflammatory cytokines, thereby connecting ER stress-triggered apoptosis with inflammatory mechanisms. CASP12 dysfunction has been associated with chronic pathologies, including cancer. The other immune-mediated cascade, i.e., the perforin 1 (PRF1) and granzyme (GZM) pathways, employs granzyme A (GZMA) or GZMB to trigger apoptosis. While both induce cellular death, they utilize distinct mechanisms: GZMB facilitates caspase-

dependent apoptosis, whereas GZMA initiates cellular death through caspase-independent routes [42-44]. The GZMs employed can differ on the basis of target cell characteristics and immune context [43]. The mechanism of GZMA involves cleaving and activating substrates, including nucleoplasmin, resulting in chromatin condensation and cell death independent of the caspase cascade. Conversely, GZMB primarily drives the caspase-dependent route by cleaving substrates, including CASP3, CASP7, and the death-promoting protein BID [45]. These various apoptotic cascades ultimately converge upon a shared terminal or execution route.

Key molecular regulators of apoptosis

Mitogen-activated protein kinase/MAPK signaling has context-dependent multifunctional involvement in apoptotic regulation, affecting both cellular death and persistence mechanisms. As an evolutionarily conserved intracellular signaling cascade, the MAPK system transmits signals originating from diverse extracellular stimuli, including growth factors, stress indicators, and cytokines. The three primary MAPK subfamilies that participate in apoptotic regulation include MAPK/extracellular signal-regulated kinase (ERK), MAPK/c-Jun N-terminal kinase (JNK), and MAPK/p38 [46].

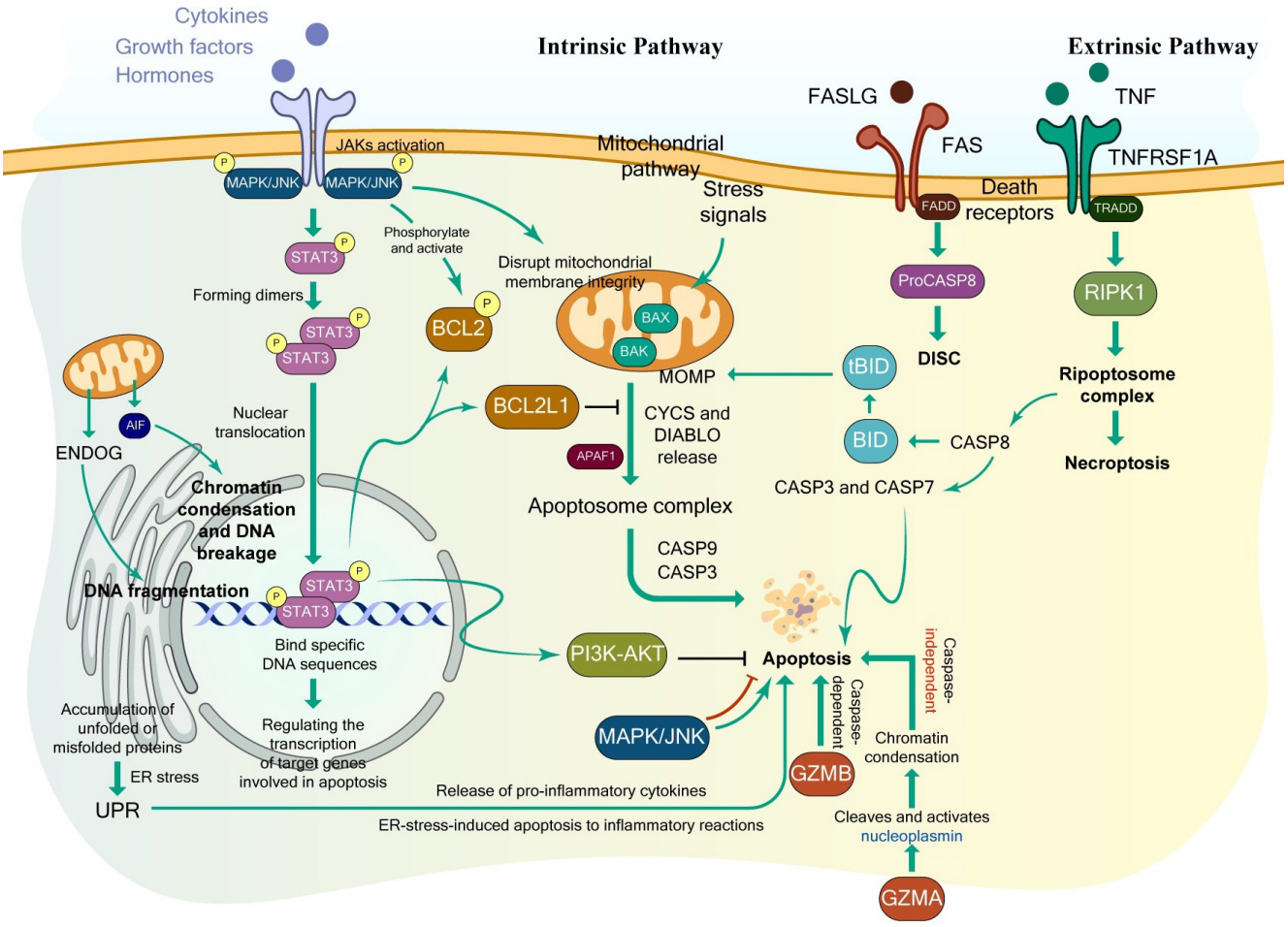


Figure 2. Schematic overview of major apoptotic signaling pathways and cross-talk mechanisms. The current diagram illustrates the core apoptotic cascades, including the intrinsic (mitochondrial) pathway, the extrinsic (death receptor) pathway, endoplasmic reticulum (ER) stress-induced apoptosis, and granzyme-mediated cell death: i) Intrinsic Pathway; intracellular stress signals induce mitochondrial outer membrane permeabilization (MOMP) via pro-apoptotic effectors BAX and BAK1. This triggers the release of cytochrome c (CYCS) and DIABLO/Smac, driving apoptosome formation alongside APAF1, which activates downstream executioner caspases (CASP9 and CASP3). Caspase-independent mitochondrial pathways are mediated by ENDOG and AIF, which translocate to the nucleus to induce chromatin condensation and DNA fragmentation. Survival and regulatory signals modulate this axis: cytokine/growth factor/hormone-receptor signaling via JAKs promotes phosphorylation of MAPK/JNK and STAT3 dimerization. Dimerized STAT3 translocates to the nucleus to regulate transcriptional programs, including anti-apoptotic BCL2 and BCL2L1 (which inhibit APAF1/MOMP) and the PI3K-AKT survival pathway. MAPK/JNK activation also phosphorylates BCL2 directly or disrupts mitochondrial membrane integrity. ii) Extrinsic Pathway; engagement of cell-surface death receptors (FAS by FASLG, and TNFRSF1A by TNF) recruits adaptor proteins FADD and TRADD. FADD assembles the death-inducing signaling complex (DISC) with ProCASP8, generating active CASP8. CASP8 directly activates executioner caspases (CASP3 and CASP7) and cleaves BID into truncated BID (tBID), bridging the extrinsic signal to mitochondrial MOMP. Alternatively, TRADD recruitment through TNFRSF1A engages RIPK1 to form the ripoptosome complex, mediating necroptosis. iii) ER Stress and Granzyme Pathways: Accumulation of unfolded or misfolded proteins inside the endoplasmic reticulum activates the unfolded protein response (UPR), linking ER stress to inflammatory responses, cytokine release, and apoptosis. Cytotoxic lymphocyte effector granzymes trigger cell death via distinct mechanisms: Granzyme B (GZMB) drives caspase-dependent apoptosis, whereas Granzyme A (GZMA) acts in a caspase-independent manner by cleaving and activating nucleoplasmin to initiate chromatin condensation.

Under certain conditions, MAPK/ERK activation facilitates cellular persistence while actively preventing apoptosis [46]. This protective mechanism operates by increasing the levels of survival-promoting proteins, including BCL2 family constituents, or by suppressing death-inducing elements.

The MAPK/JNK cascade can either increase survival or initiate apoptosis, depending upon the cellular context and the stimuli encountered. MAPK/JNK activation is commonly associated with stress-triggered apoptosis, as MAPK/JNK can phosphorylate and activate death-promoting BCL2 proteins, compromise mitochondrial membrane stability, and facilitate the liberation of death-accelerating factors [46, 47].

Interconnected communication between these MAPK cascades introduces additional regulatory complexity; for example, MAPK/ERK activation may oppose MAPK/JNK-triggered apoptosis, highlighting the intricate balance between persistent and demise signals [48, 49]. Additionally, feedback regulatory circuits involving phosphatases and negative modulators precisely govern MAPK signaling intensity and temporal duration [50]. This meticulous regulation prevents sustained or excessive activation, potentially causing inappropriate cellular death. MAPKs also play integral roles in signal transmission from death receptors, including FAS and tumor necrosis factor (TNF)/TNF-α receptors, by activating downstream caspases and regulating death-promoting BCL2 constituents [48]. The influence of MAPK signaling on apoptosis is highly intricate and context-specific reflecting sophisticated regulatory networks governing cellular destiny [48].

Caspases are the other central regulators of apoptosis and function within both the mitochondrial and death receptor pathways. They are grouped into developmental, inflammatory, and apoptotic categories [51]. Apoptotic caspases are further classified into initiator caspases (e.g., CASP8 and CASP9) and executioner caspases (e.g., CASP3, CASP6, and CASP7) [52, 53]. Initiator caspases autoactivate and subsequently cleave downstream executioner caspases, leading to complete proteolytic dismantling of the cell [54, 55].

Upon apoptotic stimulation, BH3-only proteins activate BAX and BAK1, promoting the release of CYCS and DIABLO/Smac from mitochondria and triggering apoptosome formation [56-59]. The apoptosome activates CASP9, which then initiates the CASP3 cascade, culminating in cell death [60, 61]. DIABLO and HTRA2/Omi neutralize inhibitors of apoptosis (IAPs), increasing caspase activity, whereas AIFM1/AIF (apoptosis-inducing factor mitochondria associated 1) also contributes to cell death [62-66]. Understanding these molecular events is key to clarifying disease mechanisms and guiding drug design to target apoptotic dysregulation.

The intrinsic pathway is activated by internal stressors such as reactive oxygen species (ROS), DNA damage, ER stress, cytoskeletal disruption, or growth factor deprivation [67, 68]. Classical apoptotic features include DNA fragmentation, chromatin condensation, membrane asymmetry loss, and blebbing, which depend on caspase activity [69]. Caspase activation centers on mitochondrial outer membrane permeabilization/MOMP, a critical "point of no return" that releases pro-death factors [69]. CYCS binds to APAF1, forming the apoptosome, which activates CASP9 and subsequently executioner caspases [70].

AIFM, another mitochondrial protein, translocates to the nucleus to induce chromatin condensation and DNA fragmentation in a caspase-independent manner [71]. DIABLO enhances apoptosis by binding to the BIR domains of IAPs such as XIAP, relieving their caspase inhibition [72, 73]. ENDOG (endonuclease G) and HTRA2 further promote apoptosis by facilitating DNA fragmentation and IAP antagonism [74]. The balance between pro- and antiapoptotic BCL2 family members ultimately determines survival versus death, representing a critical therapeutic target in cancer [75].

The mitochondrial intermembrane space contains numerous prodeath factors, with CYCS being the first identified. Their release is tightly controlled by heat shock proteins (HSPs) and culminates in the activation of CASP3 and other effector caspases, which execute the final biochemical and morphological features of apoptosis [76-78]. Upon release, DIABLO and HTRA2/Omi expose IAP-binding N-terminal motifs that neutralize IAPs, further promoting cell death [79-81].

Apoptosome assembly represents a pivotal step in intrinsic apoptosis [82]; CYCS released by mitochondrial stress binds to APAF1, inducing its oligomerization into a heptameric apoptosome complex [83-85]. This structure recruits and activates proCASP9, which autocatalytically matures into active CASP9 [86, 87]. CASP9 then triggers downstream activation of CASP3 and CASP7, executing apoptosis [88]. This tightly regulated cascade maintains tissue homeostasis and eliminates damaged or unwanted cells.

Activated FADD-bound CASP8 also triggers executioner caspases (CASP3, CASP7) and cleaves BID into truncated BID (tBID), linking the extrinsic and intrinsic pathways via mitochondrial outer membrane permeabilization [89]. TRADD can alternatively

recruit RIPK1 to form the ripoptosome, connecting apoptosis and necroptosis signaling [90]. These interconnections ensure flexible control of cell fate under varying stress conditions, with ER stress pathways also contributing to apoptosis in specific contexts.

TP53/p53 serves as the "guardian of the genome," orchestrating DNA repair, cell cycle arrest, or apoptosis through the transcriptional activation of targets such as *BAX*, *BBC3/PUMA*, and *PMAIP1/NOXA* [91-105]. Its activity is restrained by MDM2 under normal conditions but is stabilized upon stress [106], preventing tumorigenesis. Mutations in *TP53* impair this regulation, driving cancer progression [107, 108].

Non-caspase proteases such as calpains, cathepsins, granzymes, and proteasomes also modulate apoptosis [69, 109]. Calpains, calcium-dependent enzymes, are activated by specific intracellular Ca^{2+} concentrations, linking calcium dysregulation to apoptotic cell death [69, 110, 111].

Together, these molecular networks ensure the precise control of cellular fate. Disruption of apoptotic regulation contributes to cancer development, underscoring the importance of understanding and therapeutically targeting these pathways.

For a more comprehensive overview of the upstream regulatory complexes, domain architectures, and downstream execution nodes governing apoptosis-related pathways, see **Figure 2.**

Autophagy

Autophagy is an essential, evolutionarily conserved catabolic process responsible for degrading damaged intracellular components and recycling metabolites such as glucose, ATP, amino acids, and fatty acids [112]. It operates alongside the ubiquitin-proteasome system and is classified into three forms: chaperone-mediated autophagy/CMA, microautophagy, and macroautophagy. All of these forms deliver cytoplasmic cargo to lysosomes, although they differ in their sequestration mechanisms [113, 114]. CMA uniquely depends on proteins such as HSPA8/HSC70 (heat shock protein family A member 8) and LAMP2A (lysosomal associated membrane protein 2A) for lysosomal targeting [115]. Microautophagy internalizes cargo directly through lysosomal membrane invagination [116], whereas macroautophagy proceeds through sequential stages, initiation, nucleation, elongation, maturation, fusion, and degradation, which are regulated by a complex molecular network [114].

Macroautophagy is governed primarily by the canonical ULK1 (unc-51 like autophagy activating kinase 1) pathway, the class III PtdIns3K (phosphatidylinositol 3-kinase) complex, the LC3 (microtubule associated protein 1 light chain 3) conjugation system, and lysosomal hydrolases [117]. Stress signals activate ULK1 to initiate autophagy [118-120]. Nucleation follows through the PtdIns3K complex containing PIK3C3/VPS34, generating the phagophore. Expansion and autophagosome formation require the ATG12-ATG5-ATG16L1 complex, which mediates LC3 lipidation and membrane closure [121]. Upon fusion with lysosomes, the autolysosome, where hydrolases degrade cargo, is formed [122].

Pharmacologic inhibitors, including ULK1 inhibitors (initiation), class III PtdIns3K inhibitors (nucleation), and lysosomotropic agents that block autophagosome-lysosome fusion, target multiple stages. MTOR (mechanistic target of rapamycin kinase) and AMPK serve as central metabolic regulators of autophagy [123, 124]. MTOR suppresses autophagy under nutrient-rich conditions [124-126], whereas AMPK activates ULK1 and BECN1 during energy stress, promoting autophagy initiation [127-131]. Autophagy exerts context-dependent effects on malignancy and is influenced by tumor type, stage, and genetic background [132]. It can mediate cytotoxic autophagic cell death (type II RCD) [133-135] or support cytoprotective survival pathways that drive drug resistance [136].

Conversely, established tumors exploit autophagy to survive metabolic stress, maintain energy balance, and resist therapy [137-139]. Upregulated autophagy enhances nutrient recycling, conferring a growth advantage and promoting therapeutic resistance.

A more detailed, step-by-step schematic of the upstream metabolic cues, membrane nucleation events, and progressive vesicular transitions governing macroautophagy is illustrated in **Figure 3**.

Necroptosis

Unlike standard apoptotic cell death, necroptosis is a controlled form of cell death that does not rely on caspase enzymes. Instead, it is driven primarily by three key proteins, including receptor-interacting proteins 1 and 3 (RIP1 & RIP3) and mixed lineage kinase domain-like protein (MLKL). Because it bypasses traditional death pathways, it offers a powerful backup plan for destroying treatment-resistant cancer cells while simultaneously initiating a strong immune response against tumors [140].

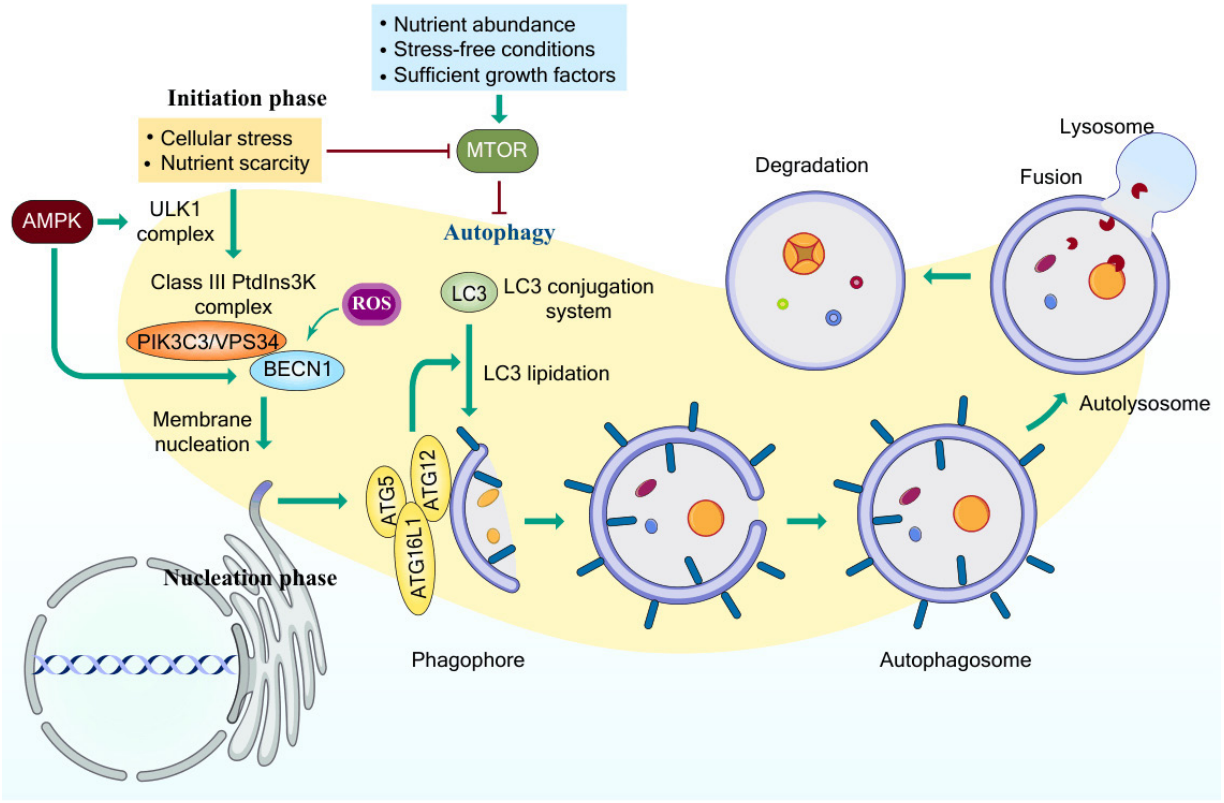


Figure 3. Molecular mechanisms and sequential stages of the autophagic pathway. Autophagy is tightly regulated upstream by metabolic and environmental cues, wherein conditions such as nutrient abundance, stress-free environments, and sufficient growth factors stimulate MTOR to suppress pathway activity. Conversely, cellular stress and nutrient scarcity alleviate MTOR-mediated repression while activating AMPK, driving initiation via the ULK1 complex. During the subsequent nucleation phase, AMPK, ULK1, and reactive oxygen species (ROS) promote activation of the Class III PtdIns3K complex, comprising PIK3C3/VPS34 and BECN1, to trigger membrane nucleation at endoplasmic reticulum-associated sites. Phagophore elongation and maturation are orchestrated by the ATG12-ATG5-ATG16L1 complex alongside the LC3 conjugation system, which drives LC3 lipidation and incorporation into the growing phagophore membrane to sequester cytoplasmic cargo within a double-membraned autophagosome. Upon completion, the autophagosome undergoes fusion with a lysosome to form an autolysosome, culminating in the degradation of enclosed contents by lysosomal hydrolases to facilitate macromolecular recycling and energy homeostasis.

Necroptosis can be initiated by a wide spectrum of upstream cues; these include members of the tumor necrosis factor receptor (TNFR) superfamily, pattern-recognition receptors (PRRs), T-cell receptors (TCRs), and several cytotoxic chemotherapeutic agents [140, 141]. Environmental stressors such as hypoxia may also activate this pathway, although malignant cells can reportedly evade hypoxia-driven necroptosis through increased glucose uptake and accelerated anaerobic glycolysis [142]. Among these diverse inducers, the TNF-TNFR1 axis remains the prototypical and most thoroughly characterized model [143]. Thus, the fundamental principles of necroptotic initiation are best illustrated through TNF-dependent signaling.

The binding of TNF to TNFR1 induces a conformational rearrangement of TNFR1 homotrimers, promoting the formation of a membrane-associated multiprotein signaling hub termed complex I [144]. This platform recruits several key regulators, including RIPK1, TNFR-associated death domain protein (TRADD), the cellular inhibitors of apoptosis cIAP1/2, and the TNFR-associated factors TRAF2/5. Within this complex, RIPK1 functions as a central determinant of cell fate [145] and undergoes BIRC2/BIRC3-mediated polyubiquitination, a modification that activates canonical NFKB signaling [143]. NFKB then induces the transcription of cytoprotective genes that promote cell survival [144].

Following rapid internalization of the ligand-bound receptor, complex I undergoes compositional and post-translational remodeling [143]. The deubiquitinase CYLD removes ubiquitin chains from RIP1/RIPK1, thereby attenuating sustained NFKB activation and shifting the signaling balance toward cell death [146]. This complex, which is composed of RIPK1, TRADD, CASP8, and FADD, facilitates CASP8 activation [147].

Complex II represents a pivotal checkpoint that dictates whether the cell is undergoing apoptosis or necroptosis. Under physiological conditions, active CASP8 cleaves and inactivates RIPK1 and RIPK3, thereby dismantling the necroptotic machinery and promoting apoptotic execution [148]. CASP8 also supports cell survival by cleaving CYLD, preventing excessive deubiquitination of RIPK1 [149]. However,

when CASP8 is genetically absent or pharmacologically inhibited [144], RIP kinase cleavage is blocked, irrevocably diverting the cell toward necroptosis.

Commitment to necroptosis is marked by RIPK1 auto-phosphorylation at serine 161 (S161), which activates its kinase function [150]. Activated RIPK1 then engages RIPK3 through their RIP homotypic interaction motifs (RHIMs), forming an amyloid-like heterodimeric assembly known as the necrosome, the central signaling scaffold for necroptosis [145].

Mitochondrial ROS further potentiate this process. ROS accumulation enhances RIPK1 auto-phosphorylation and accelerates RIPK3 recruitment, whereas RIPK3 itself promotes ROS generation, establishing a self-reinforcing positive feedback loop that ensures robust necroptotic activation [151]. CYLD additionally strengthens necrosome signaling by deubiquitinating RIPK1 after its incorporation into the complex [152]. This pathway can be pharmacologically interrupted via the use of RIPK1 inhibitors such as necrostatin-1 (Nec-1), the MLKL inhibitor necrosulfonamide (NSA), or various RIPK3-targeting small molecules [153].

Within the necrosome, activated RIPK3 phosphorylates its downstream effector, MLKL. Phosphorylated MLKL oligomerizes and translocates to the inner leaflet of the plasma membrane, where it disrupts membrane integrity. This culminates in a lytic form of cell death characterized by cellular swelling, organelle breakdown, and catastrophic membrane rupture [154, 155].

Collectively, these findings illustrate that necroptosis is a tightly regulated, multi-step death program in which upstream receptor signaling, the RIPK1 ubiquitination status, CASP8 activity, and necrosome assembly converge to determine the cellular fate. Once CASP8 inhibition permits RIPK1-RIPK3 complex formation, the necroptotic cascade becomes self-reinforcing through ROS-driven amplification, ultimately culminating in MLKL activation, membrane permeabilization, and lytic cell death. This mechanistic framework underscores necroptosis as a decisive alternative to apoptosis and highlights multiple regulatory nodes, particularly within the RIPK1-RIPK3-MLKL axis, that may be exploited for therapeutic intervention.

A detailed molecular schematic outlining the specific protein complexes, post-translational modifications, and domain interactions across the necroptotic signaling cascade is provided in **Figure 4**.

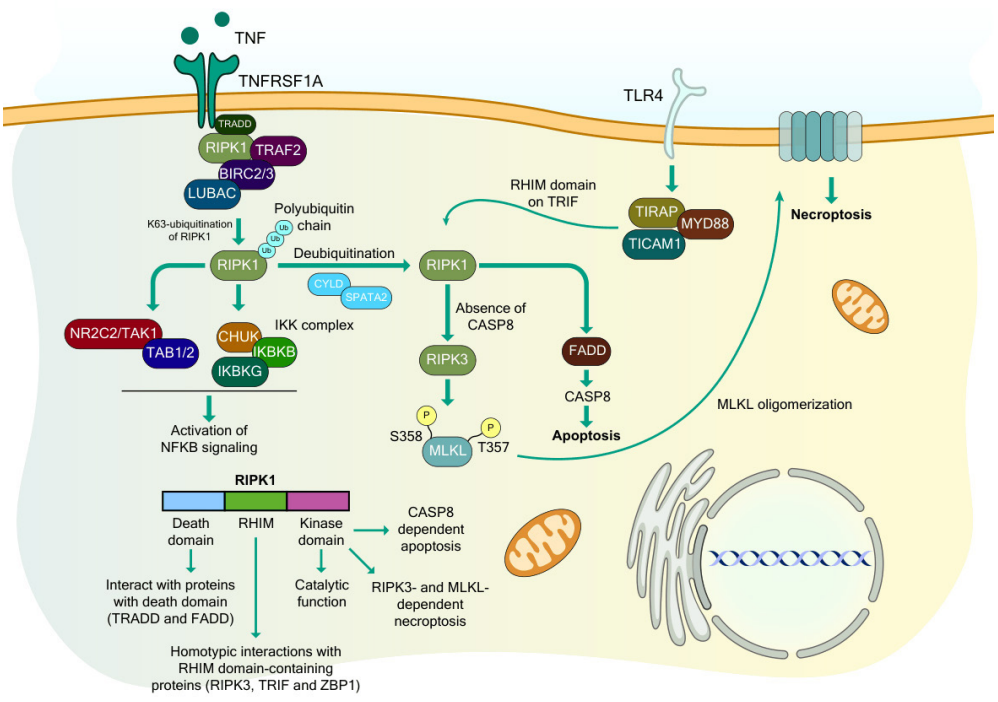


Figure 4. Receptor-mediated signaling networks orchestrating NFKB survival, apoptosis, and necroptosis. Binding of TNF to TNFRSF1A recruits a membrane-proximal complex comprising TRADD, RIPK1, TRAF2, BIRC2/3, and LUBAC, which mediates K63-linked polyubiquitination of RIPK1 to recruit and activate NR2C2/TAK1-TAB1/2 and the IKK complex (CHUK, IKBKB, and IKBKG), thereby driving NFKB survival signaling. Deubiquitination of RIPK1 by the CYLD–SPATA2 complex triggers a transition from survival to cell death pathways, a process also engaged via TLR4 through TIRAP, MYD88, and TICAM1/TRIF via its RHIM domain. In the presence of CASP8, deubiquitinated RIPK1 associates with FADD to activate CASP8, executing apoptosis. Conversely, in the absence or inhibition of CASP8, RIPK1 interacts with RIPK3 to promote downstream phosphorylation of MLKL at residues S358 and T357, driving MLKL oligomerization and plasma membrane translocation to execute necroptosis. Structurally, RIPK1 coordinates these divergent fates through distinct functional modules: its C-terminal death domain mediates interactions with death domain-containing adaptors (TRADD and FADD), the central RHIM domain facilitates homotypic assemblies with RHIM-containing partners (RIPK3, TRIF, and ZBP1), and the N-terminal kinase domain provides catalytic activity critical for both CASP8-dependent apoptosis and RIPK3/MLKL-dependent necroptosis.

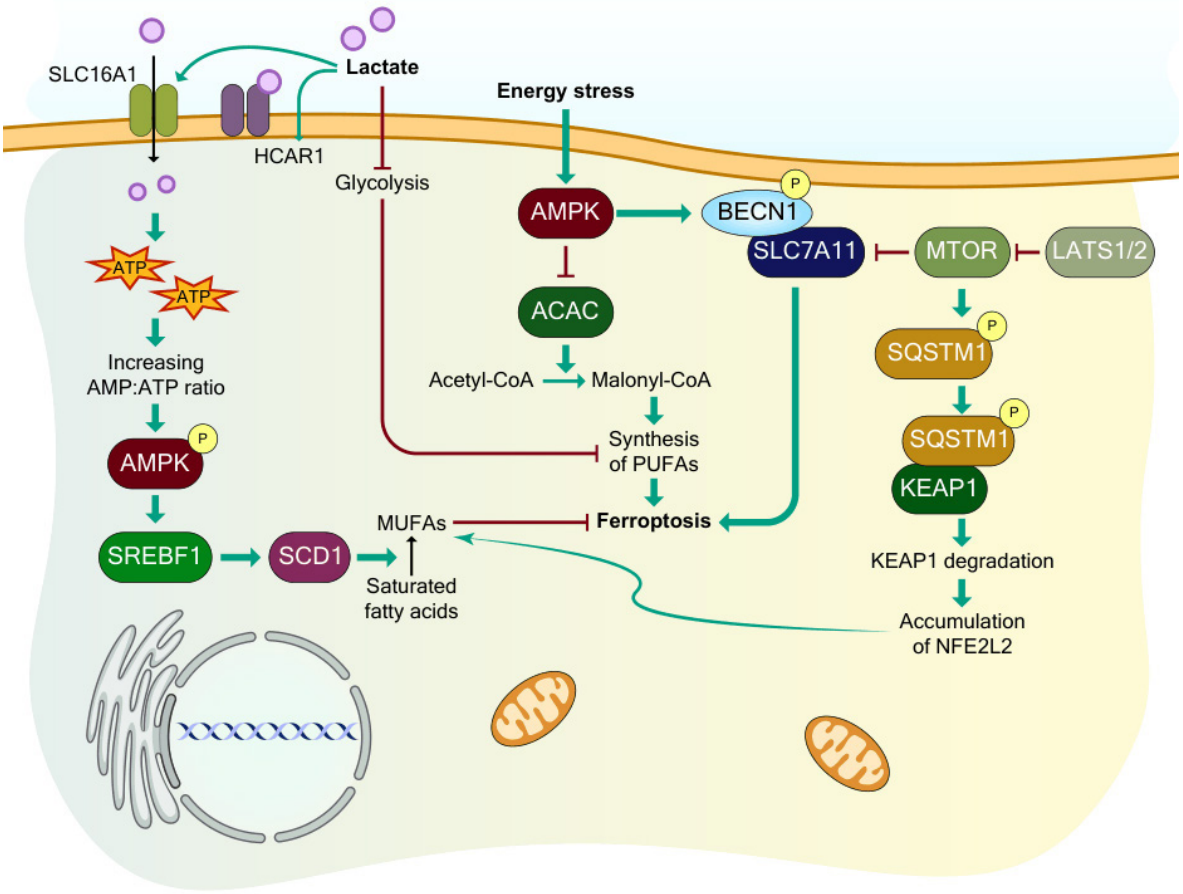


Figure 5. Metabolic and signaling networks governing ferroptosis sensitivity and resistance. Intracellular and microenvironmental metabolic pathways tightly modulate ferroptotic cell death through lipid remodeling, nutrient sensing, and redox regulation. Glycolysis-derived lactate, transported or signaled via SLC16A1 and HCAR1, depletes ATP and elevates the AMP:ATP ratio, driving phosphorylation and activation of AMPK. Activated AMPK subsequently stimulates the SREBF1–SCD1 axis to convert saturated fatty acids into monounsaturated fatty acids (MUFAs), which potently suppress ferroptosis, while glycolytic flux concurrently inhibits polyunsaturated fatty acid (PUFA) synthesis. Under cellular energy stress, AMPK independently suppresses ACAC (acetyl-CoA carboxylase) activity to prevent the conversion of acetyl-CoA to malonyl-CoA, thereby attenuating PUFA biosynthesis and limiting ferroptotic susceptibility. Concurrently, energy-activated AMPK induces BECN1 phosphorylation, which directly inhibits the cystine/glutamate antiporter SLC7A11 to promote ferroptosis. In parallel, the upstream Hippo kinase LATS1/2 represses MTOR, which otherwise negatively regulates SLC7A11 while phosphorylating SQSTM1/p62. Phosphorylated SQSTM1 complexes with and directs KEAP1 for degradation, promoting the stabilization and accumulation of NFE2L2/NRF2, which upregulates protective MUFA generation to inhibit ferroptosis.

Ferroptosis

Ferroptosis is an RCD process driven by lipid peroxidation when the level of ROS exceeds the detoxifying capacity of glutathione (GSH) and glutathione peroxidase 4 (GPX4). Although iron, lipids, and ROS are essential for cellular metabolism, their imbalance, especially under metabolic stress, initiates ferroptosis. This pathway is increasingly recognized as central to malignant biology and is implicated in cancer, neurodegeneration, and inflammatory disorders [156] (see **Figure 5** for more details). Cancer cells exhibit metabolic plasticity that can both promote survival and create vulnerabilities to ferroptosis, offering therapeutic opportunities, including synergy with immune-based treatments. However, its clinical translation remains limited [157]. Energy depletion decreases ATP levels and activates AMPK, a key metabolic sensor. AMPK suppresses ACAC1/ACC1 and ACACB/ACC2, reducing malonyl-CoA production and limiting PUFA (polyunsaturated fatty acid) synthesis, thereby decreasing ferroptosis sensitivity [158]. AMPK also phosphorylates BECN1, enabling interaction with SLC7A11 and inhibiting the system Xc^- antiporter, a paradoxical pro-ferroptotic effect [159]. These dual roles suggest that tumor cells exploit AMPK signaling to evade ferroptosis, while targeted modulation may enhance therapy.

Lactate-loaded HCC cells resist ferroptosis triggered by standard agents like RSL3 and erastin. MCT1-mediated lactate influx fuels ATP generation while blunting AMPK activity, which in turn lifts SREBP1 and its downstream effector SCD1, boosting the supply of monounsaturated fatty acids/MUFAs that shield membranes from ferroptotic peroxidation. Conversely, blocking lactate uptake through HCAR1/MCT1 inhibition re-engages AMPK, suppresses SCD1, and promotes ferroptosis, an effect that may be compounded by concurrent ACSL4

induction, sharply increasing ferroptotic sensitivity [160, 161]. MUFAs resist peroxidation, reducing susceptibility to ferroptosis [162].

Both MTORC1 and MTORC2 (MTOR complexes 1 and 2) regulate ferroptosis; MTORC2 phosphorylates SLC7A11 at Ser26, reducing its transport activity [163]. Work from the Hippo field has uncovered a direct molecular bridge between this growth-suppressive cascade and the nutrient-sensing machinery of MTORC1; the LATS1/2 kinases, which serve as the catalytic core of the Hippo pathway, act on RAPTOR, an obligatory subunit of MTORC1, by phosphorylating its Ser606 residue. This modification restrains MTORC1 activity, and it does so by disrupting the ability of RPTOR to engage RHEB. Genetic evidence reinforces the model; a phosphomimetic knock-in allele, RPTOR-S606D, produces cells of reduced size that divide less readily. Thereby, these findings position the Hippo and MTORC1 pathways in direct communication, providing a mechanism through which organ size can be tuned with precision [164]. The PI3K-AKT-MTOR cascade, which is frequently altered in cancer, enhances MUFA synthesis via SREBF1, promoting ferroptosis resistance [162].

Cancer cells experience increased oxidative stress, which activates NFE2L2/NRF2 (NFE2-like bZIP transcription factor 2), which induces antioxidant response element (ARE)-containing genes [165]. Mutations in KEAP1, CUL3, or NFE2L2 stabilize NFE2L2, increasing its nuclear accumulation in conditions such as non-small cell lung cancer (NSCLC) and lung squamous cell carcinoma (LSCC) [166, 167].

Despite high metabolic demand, dense growth, and oxidative stress, conditions that favor ferroptosis, tumor cells rarely undergo spontaneous ferroptotic death. This reflects robust compensatory mechanisms involving metabolic rewiring, antioxidant activation, and cell-density signaling. Understanding how ferroptosis interfaces with classical oncogenic pathways is essential for developing therapies that selectively activate ferroptosis and overcome current treatment limitations. A comprehensive overview of the metabolic circuits, upstream oncogenic cascades, and lipid-peroxidation checkpoints governing ferroptosis sensitivity is depicted in **Figure 5**.

Pyroptosis

Pyroptosis is an inflammatory form of RCD mediated by the gasdermin/GSDM family of pore-forming proteins, including GSDMA-GSDME. Upon activation by caspases or granzyme proteases, the amino-terminal GSDM fragment inserts into cellular membranes to form pores, inducing pyroptosis. Although GSDMs have been widely studied in cancer, their overall contribution remains context-dependent, as both pro-tumorigenic and anti-tumorigenic effects have been reported. Pyroptosis can be triggered by pathogen-associated molecular patterns (PAMPs), DAMPs, and various chemotherapeutic agents in GSDM-expressing cells [168].

Inflammasomes are multiprotein complexes activated by intracellular stress or pathogens. Key sensors include MEFV/pyrin, AIM2, and several NLRs (NOD-like receptors), such as NLRP1, NLRP3, and NLRC4 [169]. Among these proteins, NLRP3 is the most extensively characterized.

NLRP3 promotes tumor progression by enhancing the proliferation and motility of A549 lung cancer cells [170], correlates with disease progression in oral squamous cell carcinoma (OSCC) [171], and drives EMT in colon cancer independent of inflammasome activation [172]. It also contributes to chemoresistance in OSCC [173]. Inflammasome/NLRP3-associated secretion of IL18 supports proliferation, immunosuppression, angiogenesis, and metastasis across cancers like lymphoma and gastric cancer [174, 175]. Similarly, NLRP1 enhances melanoma progression by promoting inflammasome activity and inhibiting apoptosis [176].

Conversely, reduced expression of NLRP3, NLRP1, and AIM2 in hepatocellular carcinoma (HCC), colorectal cancer (CRC), and gastric cancer (GC) is correlated with advanced disease, suggesting that tumor-suppressive effects are involved [177-179]. In colitis-associated cancer, NLRP3-driven IL18 protects intestinal epithelial cells from DSS- or AOM-induced injury [180-183]. NLRC4 in tumor-associated macrophages (TAMs) suppresses melanoma growth independently of inflammasome activation [184], whereas NLRP3 in Kupffer cells limits CRC liver metastasis by promoting NK cell maturation and IL18-dependent cytotoxicity [185].

The GSDM family (GSDMA-GSDME) has diverse, tumor-specific functions; GSDMA, expressed mainly in epithelial tissues, is linked to TNF-induced apoptosis [186], and skin inflammation and alopecia [187, 188]. Its frequent silencing in gastric cancer suggests a tumor- suppressive role [189]. GSDMB is often overexpressed in cancers such as breast cancer, where it promotes migration, metastasis, and therapy resistance, particularly in ERBB2/HER2$^+$ breast cancer [190, 191]. GSDMC is upregulated in CRC due to TGFBR2 mutation [192] and is associated with poor prognosis in lung adenocarcinoma [193].

GSDMD, a central innate immune mediator, has dual effects: it enhances NSCLC aggressiveness via EGFR-AKT signaling [194] but suppresses gastric

cancer progression by regulating the S-to-G2 transition [195]. Several agents, such as α-NETA [196], and polyphyllin VI [197], induce GSDMD-dependent pyroptosis, inhibiting tumor growth. Metformin also triggers pyroptosis in ESCC through the MIR497-PELP1 axis [198]. CARD8-mediated pyroptosis via DPP8/9 inhibition has been proposed as a therapeutic strategy in AML [199], whereas CD38 deficiency reduces inflammasome-driven pyroptosis in HNSCC [200].

GSDME/DFNA5 has highly context-specific roles; however, a novel DFNA5 mutation (IVS8+4 A>G) in the splice donor site of intron 8 has been found to cause late-onset non-syndromic hearing loss in a Chinese family [201, 202]. GSDME is frequently silenced by promoter hypermethylation in breast [203, 204] and colorectal [205-207] cancers, which is correlated with poor prognosis. Restoring GSDME expression suppresses proliferation [206, 208] and increases chemosensitivity, such as in retinoblastoma [209]. However, some studies have reported no association between GSDME methylation and tumorigenesis. Chemotherapy-induced CASP3 cleavage of GSDME triggers pyroptosis [210, 211], enhancing cisplatin sensitivity in some contexts [211], although not universally.

Overall, GSDMs exert heterogeneous, tumor-dependent effects; some (e.g., GSDME) act as suppressors, whereas others (e.g., GSDMB and GSDMC) promote malignancy. Pyroptosis in hypoxic tumor regions may paradoxically sustain inflammation and tumor progression. In addition to pyroptosis, other pyroptosis-independent functions of GSDMs require further study. For a more detailed overview of the proteolytic cascades, gasdermin pore-forming complexes, and drug-induced pyroptotic pathways in cancer, see **Figure 6**.

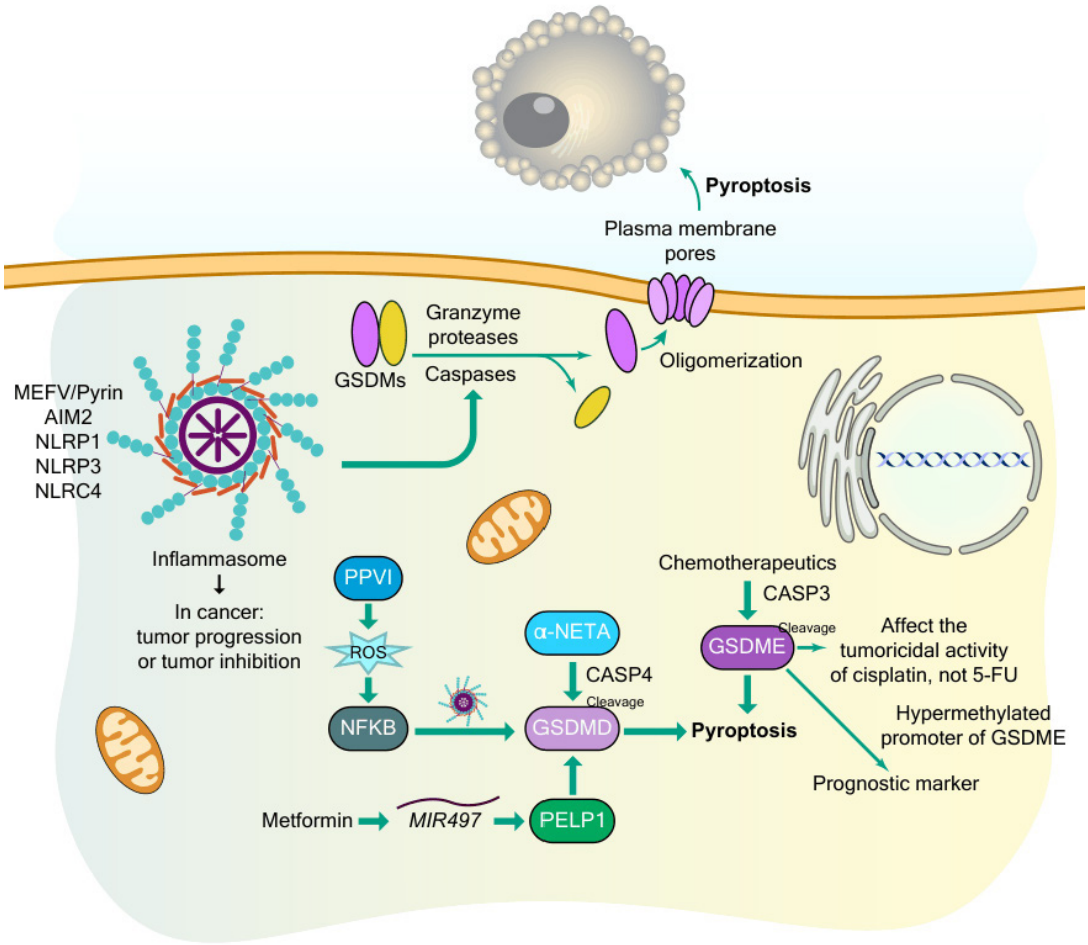


Figure 6. Mechanistic pathways, molecular regulators, and clinical implications of pyroptotic cell death in cancer. Canonical and non-canonical pyroptosis execution relies on the proteolytic cleavage of gasdermin family members (GSDMs) by inflammatory caspases or granzyme proteases, releasing active N-terminal domains that oligomerize to form lytic plasma membrane pores. Upstream inflammasome complexes, including MEFV/Pyrin, AIM2, NLRP1, NLRP3, and NLRC4, direct caspase activation to govern contextual tumor progression or suppression. GSDMD-mediated pyroptosis is regulated via multiple pharmacological and signaling axes: polyphyllin VI (PPVI) stimulates reactive oxygen species (ROS) production to drive NFKB signaling and inflammasome assembly, α-NETA engages CASP4-mediated cleavage of GSDMD, and metformin modulates the *MIR497*-PELP1 axis to promote GSDMD activity. Concurrently, chemotherapeutic agents induce CASP3-dependent cleavage of GSDME to trigger pyroptosis, modulating the tumoricidal efficacy of cisplatin without altering sensitivity to 5-fluorouracil (5-FU). In clinical contexts, hypermethylation of the *GSDME* promoter serves as an informative prognostic biomarker across malignancies.

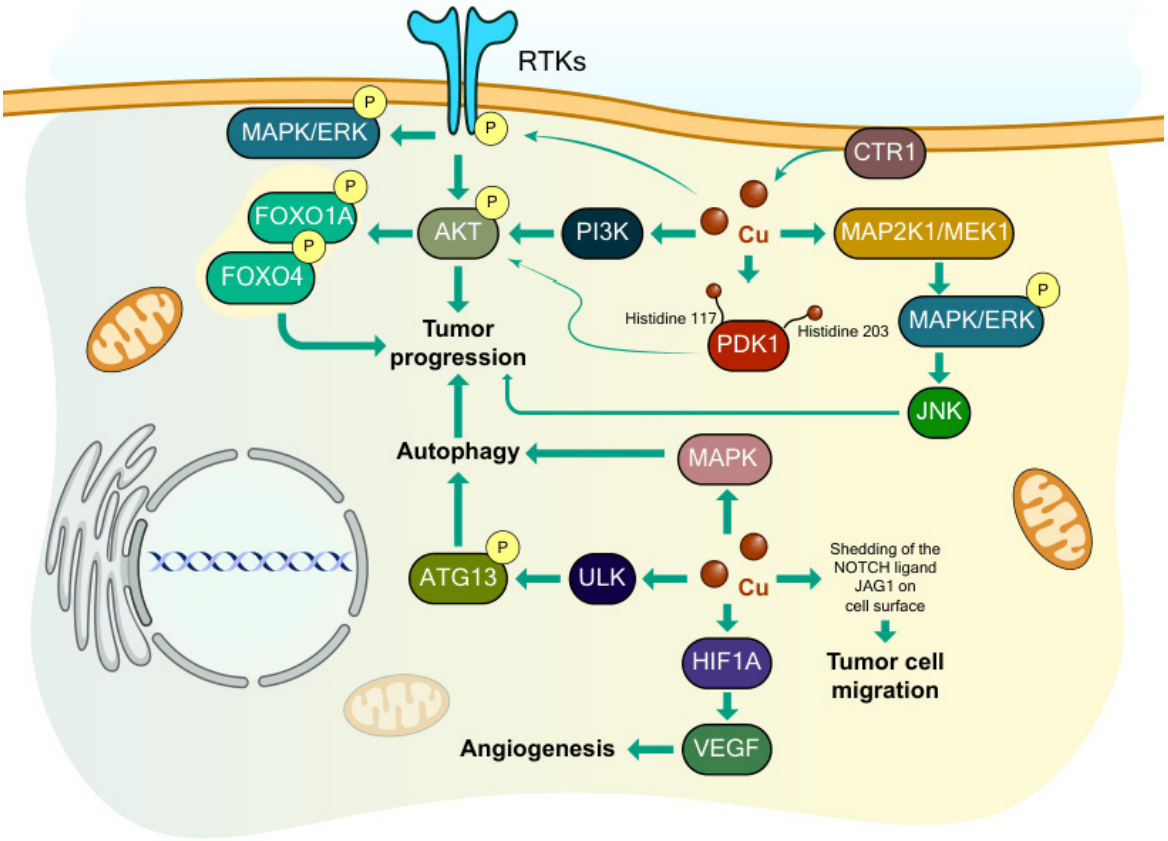


Figure 7. Copper-dependent oncogenic signaling cascades modulating autophagy, tumor progression, angiogenesis, and cell migration. Intracellular uptake of copper via the high-affinity copper transporter CTR1 stimulates multiple oncogenic and metabolic pathways. Cytoplasmic copper engages receptor tyrosine kinases (RTKs) and downstream PI3K signaling while coordinating with PDK1 through histidine residues (His117 and His203) to promote AKT phosphorylation. Activated AKT directly enhances tumor progression and phosphorylates the transcription factors FOXO1A and FOXO4 to drive pro-tumorigenic cascades. In parallel, copper binding stimulates the canonical MAP2K1/MEK1-MAPK/ERK pathway, leading to downstream JNK activation that promotes tumor growth. Copper also orchestrates autophagy via two distinct routes: through activation of intermediate MAPK signaling and by directly binding ULK kinases to induce ATG13 phosphorylation. Concurrently, copper stabilizes HIF1A to upregulate VEGF expression, driving angiogenesis, while simultaneously promoting the cell-surface shedding of the NOTCH ligand JAG1 to stimulate tumor cell migration

Cuproptosis

Cuproptosis is a recently described RCD variant that is uniquely reliant on copper ions and executes through a mechanism distinct from all previously established cellular death cascades (see **Figure 7** for more details). Although extensive investigations throughout the past decade have examined diverse RCD modalities, the proposition that copper can trigger a completely separate death mechanism remained theoretical until its molecular architecture was definitively characterized [212].

Copper performs pivotal functions in multiple intracellular signaling networks within malignant cells, chiefly through its ability to engage and activate critical molecular constituents across various cascades. Copper is extensively integrated into receptor tyrosine kinase (RTK)-facilitated signaling. It can activate RTKs by engaging and phosphorylating them even without their ligands, which then initiates downstream kinases, including MAPK/ERK and AKT, facilitating cellular motility and proliferation [213].

Within the PI3K-AKT axis, copper modulates signaling through two principal mechanisms: (i) Copper directly activates PI3K, resulting in subsequent AKT activation [214]; (ii) Copper engages with histidine residues (H117 and H203) on PDK1 (pyruvate dehydrogenase kinase 1), which also results in AKT activation [215]. Activated AKT then phosphorylates the transcription factors FOXO1/FOXO1A and FOXO4, augmenting tumor cell proliferation and division [216]. Copper is also indispensable for the activation of the MAPK cascade [217]; it directly engages with MAP2K1/MEK1, enabling MAPK1/ERK2 and MAPK3/ERK1 phosphorylation and subsequent MAPK/JNK activation, which contributes to tumor advancement.

Autophagy permits malignant cells to recycle intracellular constituents, supplying energy and increasing survival. Copper regulates this mechanism by engaging with ULK, which activates ATG13 through phosphorylation, launching autophagosome

generation and supporting tumor proliferation [218]. In lung adenocarcinoma promoted by the BRAF oncogene, depletion of the copper transporter SLC31A1/CTR1 diminishes intracellular copper, compromising the operation of MAP2K1/MEK1, MAP2K2/MEK2 and ULK1/ULK2, which are essential for both MAPK and autophagy signaling [219].

Although the NOTCH cascade can function as a tumor suppressor, it is also involved in the development of aggressive malignancies [220]. Copper enables the cleavage of the NOTCH ligand JAG1/Jagged1 (jagged canonical Notch ligand 1), augmenting tumor cell migration [221]. Copper is also intimately associated with tumor angiogenesis [222]. It supports HIF1A/HIF-1α (hypoxia inducible factor 1 subunit alpha) engagement with gene promoters, regulating genes, such as HIF1A [223, 224]. Even under normoxic circumstances, copper stabilizes HIF1A, which elevates VEGF expression and facilitates blood vessel generation in tumors [225]. Copper also increases MYC/c-Myc stability by facilitating phosphorylation at threonine 58 and serine 62 [226].

With respect to metabolic regulation, copper modulates both lipid and glucose metabolism. It regulates lipolysis by engaging with cysteine residues on PDE3B, the enzyme responsible for degrading cAMP [227]. Additionally, copper is believed to suppress tumor expansion by downregulating RPS6KB1/S6K1 and its downstream glycolytic targets, including SLC2A1/GLUT1, PKM/PKM2, and LDHA" to "Additionally, disulfiram/copper complexes have been shown to suppress tumor expansion by downregulating RPS6KB1/S6K1, MYC, and downstream glycolytic targets, including SLC2A1/GLUT1, PKM/PKM2, and LDHA [228].

In conclusion, copper has multiple regulatory effects on malignant cell behavior through both direct molecular engagement and indirect modulation of the tumor microenvironment, emphasizing its critical function in oncogenic signaling and the emerging importance of cuproptosis in cancer biology. For an in-depth and more detailed molecular overview of copper-dependent kinase activation cascades, transcriptional reprogramming, and tumor-promoting pathways, see **Figure 7**.

Other nonapoptotic RCDs

Parthanatos is an RCD modality that is dependent on PARP1 and triggered by DNA damage and chromatin degradation from oxidative stress [229]. Hyperactive PARP1 induces parthanatos via metabolic depletion (NAD^+, ATP) and mitochondrial dysfunction [230], requiring AIF [231], but not caspases or ENDOG [232]. PARP1 binds AIFM1, causing mitochondrial release and nuclear translocation and inducing chromatinolysis [233]. Negative regulators include ADPRS/ADPRHL2 and RNF146 [234, 235], whereas OGG1 promotes this process [236]. MIF acts as an AIFM1-bound nuclease, generating large DNA fragments [237]. AIFM1-independent parthanatos occurs in some conditions, such as dry macular degeneration [238], and interacts with autophagy-dependent cell death and necroptosis [239, 240].

Entosis is a form of cellular cannibalism in which one cell engulfs another, as observed in epithelial tumor cells under conditions of stress, glucose deprivation, matrix detachment, or mitotic stress [241-243]. The hallmark is cell-in-cell structures [243]. Entosis can promote aneuploidy, nutrient supply, or cancer cell elimination [244-246]. Induction depends on cadherin-mediated adherens junctions (CDH1, CTNNA1), intact actin and microtubules, and RHOA-, ROCK- and myosin-regulated actomyosin contractility [241, 242, 247-250]. Other regulators, including CDC42, AURKA, AMPK, and NUPR1 negatively regulate entosis [241, 242, 251]. Engulfed cells undergo division, release, or lysosomal degradation via LC3-associated phagocytosis and CTSB, independent of caspases or BCL2 proteins [247, 252].

NETosis involves neutrophils releasing neutrophil extracellular traps (NETs) [253] and occurs in other cell types [254-256]. NETs trap pathogens and promote DAMP release, contributing to autoimmunity, ischemia-reperfusion injury, and tumor progression [257-259]. NETosis requires ROS via NOX (NADPH oxidase), granular enzyme translocation, and histone citrullination by PADI4 for chromatin decondensation and nuclear envelope disruption [260-263]. PADI4-independent pathways exist downstream of pyroptosis, necroptosis, or autophagy-dependent cell death. GSDMD can also participate in NETosis [264, 265].

Lysosome-dependent cell death (LCD) occurs via lysosomal membrane permeabilization (LMP), which releases hydrolytic enzymes into the cytosol [266]. As proposed in 1955 and named in 2000, LMP can be induced by detergents, methyl esters, lipid metabolites, and reactive oxygen species (ROS) [266] and can amplify apoptosis, autophagy-dependent cell death, or ferroptosis [267, 268]. Cathepsins are key effectors [269] that can be positively regulated by STAT3 [270] and inhibited by NFKB-induced SERPIN [271]. Furthermore, CTSB cleaves the lysosomal calcium channel MCOLN1/TRPML1 to regulate lysosomal dynamics and autophagy [272], and LMP-mediated iron release contributes to ferroptosis [267,

273, 274].

Alkaliptosis, coined in 2018, is an RCD triggered by intracellular alkalinization [275]. JTC801 induces death in multiple cancer lines through mechanisms distinct from those of other RCDs [275]. Inhibition of alkalinization blocks this death [275]. NFKB-dependent downregulation of CA9, which is controlled by IKBKB, is needed, whereas OPRL1 is dispensable [275].

Oxeiptosis is a type of caspase-independent RCD induced by ROS and is mediated via the KEAP1-PGAM5-AIFM1 pathway [276]. It was introduced in 2018 and is independent of apoptosis, pyroptosis, necroptosis, autophagy, and ferroptosis [276]. Hyperactivated KEAP1 drives H_2O_2-induced oxeiptosis, interacting with PGAM5, which dephosphorylates AIFM1 at Ser116 [276]. Unlike parthanatos, AIFM1 nuclear translocation is unnecessary [276]. *pgam5*$^{-/-}$ mice show increased inflammation after ozone or viral exposure, suggesting that oxeiptosis suppresses inflammation [276].

An in-depth comparative molecular layout detailing the distinct triggering conditions, intermediate enzymes, and terminal structural executions of parthanatos, entosis, NETosis, LCD, alkaliptosis, and oxeiptosis beyond the text is schematically depicted in **Figure 8**.

DRUG RESISTANCE: A MAJOR OBSTACLE IN CANCER TREATMENT

Cancer cells demonstrating treatment unresponsiveness or developing tolerance are subsequently designated drug resistant. This framework originated from infectious disease research, where specific bacterial populations evolved survival mechanisms against antibiotic exposure [292]. Subsequently, analogous resistance mechanisms were characterized in malignant cells, establishing drug resistance as a fundamental weakness in cancer therapeutic approaches [293]. While this phenomenon is well documented, recent scientific progress has focused on its cellular and molecular architecture [294, 295].

Drug resistance in oncology is primarily stratified into two categories, as shown in **Figure 9**: (i) Intrinsic (innate or primary) resistance, which refers to the inherent capacity of malignant cells to resist a pharmaceutical agent prior to its administration. The absence of an initial therapeutic response typically indicates this resistance form [11]. (ii) Acquired (extrinsic or secondary) resistance that emerges following treatment initiation, as malignant cells adapt through genetic alterations or protein modifications. Managing acquired resistance frequently presents greater complexity than addressing intrinsic resistance [11]. To provide a more comprehensive framework of drug resistance biology, the following sections review the major molecular mechanisms underlying chemoresistance, which are illustrated in **Figure 9** with further details.

Table 1. Classification of RCD Mechanisms and Their Functional Roles in Cancer

RCD SUBTYPE	CORE MECHANISTIC PATHWAY	PROMINENT ROLE(S) IN CANCER	REFERENCE(S)
Apoptosis	Intrinsic (mitochondrial) and extrinsic (death receptor) pathways leading to caspase activation and cellular dismantling.	Loss of apoptosis contributes to tumor initiation, progression, and therapy resistance; restoring apoptotic signaling is a major therapeutic goal.	[51, 57, 69]
Autophagy	Lysosomal degradation of damaged organelles and proteins via ULK1-PtdIns3K-LC3 pathway.	Tumor suppression by removing damaged components in early stages Tumor promotion via metabolic adaptation and drug resistance in advanced cancer.	[114, 277, 278]
Necroptosis	Caspase-independent, RIPK1-, RIPK3- and MLKL-driven cell death causing membrane rupture and inflammation.	Exhibits context-dependent effects: anti-tumor immunity activation or pro-tumor inflammation and metastasis, depending on tumor microenvironment.	[141, 279, 280]
Ferroptosis	Iron-dependent oxidative death caused by lipid peroxidation and glutathione depletion.	Induces selective death in metabolically stressed tumors; resistance mechanisms (NFE2L2, MTOR) link ferroptosis suppression to tumor survival and drug resistance.	[281-283]
Pyroptosis	GSDM-mediated pore formation triggered by inflammasome-activated caspases (e.g., CASP1, CASP4, CASP5, CASP11).	Double-edged: promotes anti-tumor immunity via immunogenic death, but chronic pyroptosis-driven inflammation can foster tumor growth and metastasis.	[284-286]
Cuproptosis	Copper-dependent protein aggregation and mitochondrial dysfunction causing proteotoxic stress.	Copper overload promotes oxidative stress and oncogenic signaling; controlled induction of cuproptosis holds therapeutic promise in copper-addicted cancers.	[287-290]
Parthanatos	PARP1 hyperactivation leading to NAD^+ and ATP depletion and AIFM1-mediated chromatinolysis.	Excessive PARP1 activity promotes cancer cell death under DNA damage; chronic activation linked to therapy-induced toxicity and resistance.	[229, 230, 232, 233, 291]
Entosis	Cell-in-cell engulfment and degradation through LC3-associated phagocytosis and lysosomal digestion.	Can suppress tumor growth by killing neighboring cells or promote progression through aneuploidy and nutrient scavenging.	[243, 249]
NETosis	Release of neutrophil extracellular traps (NETs) through ROS and histone citrullination.	NET-derived inflammation promotes tumor progression, metastasis, and immune evasion; NET inhibition may reduce metastatic spread.	[256, 261]

Alkaliptosis	NFKB-IKBKB-CA9 axis-driven intracellular alkalinization-induced death.	Emerging anti-tumor target; selective pH-dependent death in cancer cells resistant to apoptosis or ferroptosis.	[275]
Oxeiptosis	ROS-induced KEAP1-PGAM5-AIFM1-mediated caspase-independent cell death.	Anti-inflammatory cell death mechanism; may limit oxidative stress-induced inflammation in tumors.	[276]

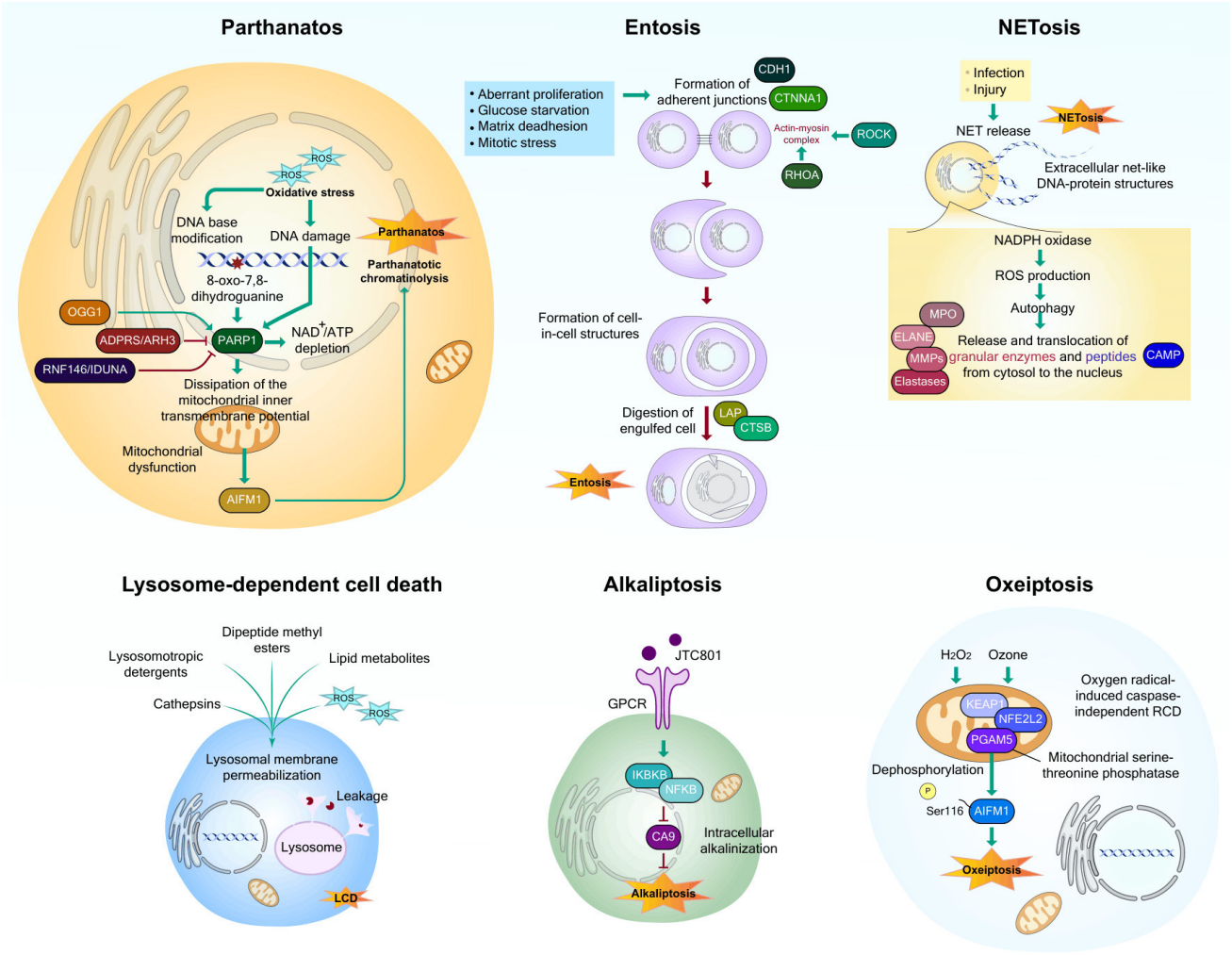


Figure 8. Mechanistic pathways and signaling networks underlying non-canonical regulated cell death modalities. Parthanatos is triggered by oxidative stress and severe DNA damage, generating base modifications such as 8-oxo-7,8-dihydroguanine that hyperactivate PARP1, a process counter-regulated by OGG1, ADPRS/ARH3, and RNF146/IDUNA. PARP1 overactivation induces severe NAD^+/ATP depletion and dissipation of the mitochondrial inner transmembrane potential, driving the release of mitochondrial AIFM1 to translocate to the nucleus and execute parthanatotic chromatinolysis and DNA fragmentation. Entosis is stimulated by triggers including aberrant proliferation, glucose starvation, matrix deadhesion, and mitotic stress, prompting adherens junction formation via CDH1 and CTNNA1 alongside RHOA/ROCK-driven actin-myosin complex contractility; this facilitates internalization into a cell-in-cell structure, followed by lysosome-associated phagocytosis (LAP) and CTSB-mediated degradation of the engulfed cell. NETosis is elicited by infection or tissue injury through NADPH oxidase-dependent ROS generation and autophagy, promoting the release and nuclear translocation of granular enzymes and antimicrobial peptides (including MPO, ELANE, MMPs, elastases, and CAMP) to extrude extracellular net-like DNA-protein structures. Lysosome-dependent cell death (LCD) results from lysosomal membrane permeabilization triggered by cathepsins, lysosomotropic detergents, dipeptide methyl esters, lipid metabolites, and ROS, causing hydrolytic enzyme leakage into the cytosol. Alkaliptosis is driven by GPCR activation via agents such as JTC801, which signals through the IKBKB–NFKB axis to downregulate carbonic anhydrase 9 (CA9), inducing lethal intracellular alkalinization. Oxeiptosis serves as an oxygen radical-induced, caspase-independent cell death cascade activated by hyperoxides or ozone, wherein the KEAP1-PGAM5-NFE2L2 sensory complex prompts the mitochondrial serine-threonine phosphatase PGAM5 to dephosphorylate AIFM1 at Ser116, culminating in mitochondrial dysfunction and oxeiptotic demise.

Mechanistic Foundations of Drug Resistance

Multiple cellular and molecular mechanisms contribute to treatment failure, including genomic instability, drug efflux, suppression of cell death pathways, drug metabolism and inactivation, EMT, epigenetic alterations, and immune evasion, as highlighted below:

Genetic modifications and chromosomal instability

Genomic instability is a hallmark of cancer and promotes tumor evolution, heterogeneity, and therapeutic resistance [296]. It includes mutations, microsatellite alterations, and chromosome instability (CIN), all of which can facilitate adaptation to therapeutic stress and are associated with poor clinical outcomes [297, 298]. Studies in multiple cancer types,

including non-small cell lung cancer and epithelial ovarian cancer, have demonstrated strong associations between CIN, intratumoral heterogeneity, disease recurrence, and resistance to anticancer therapies [299-301].

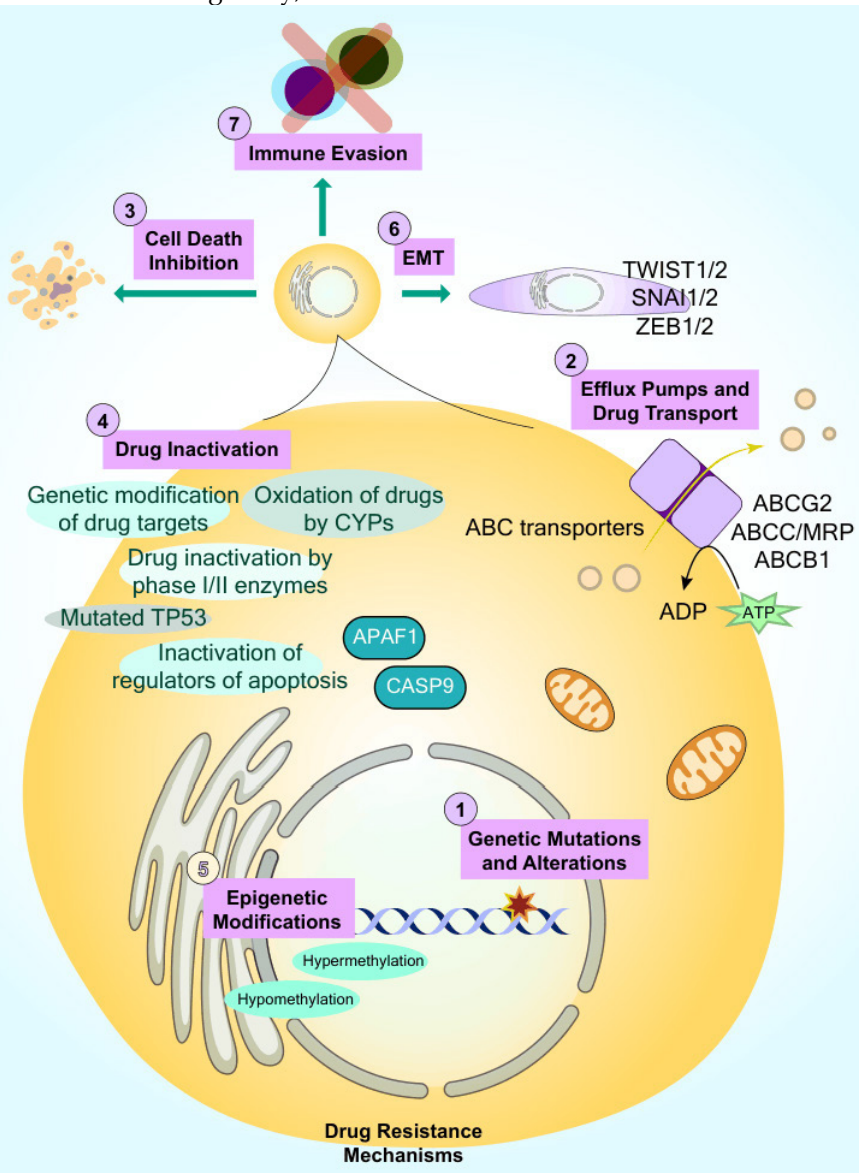


Figure 9. Multifactorial mechanisms contributing to cancer drug resistance. Tumor cells acquire therapeutic resistance through diverse intrinsic and extrinsic processes, outlined across seven primary dimensions: (1) genomic instability marked by genetic mutations and alterations; (2) enhanced drug clearance mediated by ATP-dependent efflux pumps and ABC transporters, including ABCG2, ABCC/MRP, and ABCB1; (3) suppression of cell death pathways through the inactivation of key apoptotic regulators, such as mutated TP53, APAF1, and CASP9; (4) metabolic drug inactivation driven by genetic modification of drug targets, oxidation by cytochrome P450 enzymes (CYPs), or biotransformation via phase I/II metabolizing enzymes; (5) epigenetic modifications involving aberrant DNA hypermethylation and hypomethylation patterns; (6) induction of epithelial–mesenchymal transition (EMT) orchestrated by master transcription factors TWIST1/2, SNAI1/2, and ZEB1/2; and (7) immune evasion strategies that shield resistant tumor clones from cytotoxic immune recognition and clearance.

Drug efflux transporters

Enhanced drug efflux is one of the most extensively characterized resistance mechanisms. ATP-binding cassette (ABC) transporters actively export chemotherapeutic agents from cancer cells, thereby reducing intracellular drug accumulation and efficacy [302, 303]. Among the most clinically relevant transporters are ABCB1/P-glycoprotein, ABCG2/BCRP, and members of the ABCC/MRP family [302, 304-306]. The overexpression of these transporters has been reported in numerous malignancies and is associated with resistance to different anticancer agents in different cancers, particularly breast cancer [307-309].

Suppression of regulated cell death

Evasion of regulated cell death, particularly apoptosis, represents a central mechanism of cancer

drug resistance [14]. Alterations in apoptotic regulators, including BCL2 family proteins, caspases, and inhibitor of apoptosis proteins (IAPs), enable tumor cells to survive despite therapeutic stress [28, 310]. Increased expression of antiapoptotic proteins such as BCL2 and MCL1 has been linked to resistance in several malignancies, while their inhibition can restore treatment sensitivity [311-314]. Given the pivotal role of RCD in therapeutic responses, the relationship between specific RCD modalities and drug resistance is discussed in detail in the next section.

Drug inactivation and metabolic adaptation

Cancer cells can reduce drug efficacy through alterations in drug metabolism, including increased detoxification of active compounds and impaired activation of prodrugs [315]. Enzymes such as glutathione S-transferases (GSTs), cytochrome Ps (e.g., CYP450 and CYP3A4), and UDP-glucuronosyltransferases (UGTs) play major roles in these processes [316-321]. Increased activity or altered expression of these enzymes has been associated with resistance to numerous chemotherapeutic agents.

Epithelial-to-mesenchymal transition

EMT is a reversible cellular program that enhances migration, invasion, metastatic potential, and therapeutic resistance [322-324]. EMT is regulated by transcription factors such as TWIST, ZEB, and SNAI family members and can be activated by signaling pathways, including TGFB, WNT, NOTCH, and Hedgehog [325, 326]. EMT has been implicated in resistance to multiple anticancer agents, through mechanisms involving cancer stem cell maintenance, enhanced survival signaling, and increased drug efflux [327-331].

Epigenetic alterations

Epigenetic modifications such as DNA methylation contribute substantially to cancer drug resistance by altering gene expression without changing the DNA sequence [332-334]. These mechanisms include chromatin remodeling, dysregulated noncoding RNAs (e.g., lncRNA *UCA1*), and aberrant DNA methylation patterns. These alterations can promote survival pathways, enhance drug detoxification, facilitate EMT, and modulate cellular responses to therapy, thereby contributing to treatment failure [335-338].

Immune evasion

Tumor cells employ diverse strategies to evade immune surveillance, reducing the effectiveness of both conventional therapies and immunotherapies [339, 340]. These mechanisms include impaired antigen presentation, antigen loss, activation of immune checkpoint pathways, remodeling of the tumor microenvironment, epigenetic reprogramming, and increased intratumoral heterogeneity [340-344]. Additional factors, such as antigenic drift, IDO-mediated immunosuppression, aberrant CTNNB1 signaling, and PTEN loss, further contribute to immune escape and therapeutic resistance [345-349].

In conclusion, these mechanisms interact to promote tumor survival under therapeutic pressure. While they provide important context for understanding treatment failure, the following section focuses specifically on how distinct forms of regulated cell death contribute to the development and maintenance of tumor drug resistance. The detailed convergent molecular networks underlying tumor therapeutic failure, detailing the functional coordination between membrane drug-efflux pumps, enzymatic drug neutralization, transcriptional EMT reprogramming, and cell-death evasion, are systematically mapped in **Figure 9**.

REGULATED CELL DEATH AND CANCER DRUG RESISTANCE: MECHANISTIC AND THERAPEUTIC IMPLICATIONS

Cancer cells possess a well-documented ability to bypass various cell death pathways, a hallmark of malignancy [17]. One common strategy involves the overproduction of proteins that inhibit apoptosis, preventing the initiation of cell death cascades [16]. Extensive research has clarified how RCD mechanisms contribute to cancer development and therapy resistance across experimental and clinical settings. These insights have helped identify new therapeutic targets, improve prognostic models, and guide strategies for overcoming resistance in refractory cancers. However, the pharmacodynamics of many new agents remain unclear and require further validation through preclinical and clinical studies. **Figure 10** provides a detailed and comprehensive beyond-text overview of the interplay between specific regulated cell death pathways and the molecular mechanisms underlying cancer therapy resistance. A central strategy in cancer therapy involves inducing controlled cell death within tumors [350]. By understanding and modulating diverse death pathways, treatments can selectively eliminate cancer cells while sparing normal tissue. This section reviews strategies that target apoptosis, necroptosis, autophagy, ferroptosis, and pyroptosis (**Table 2**).

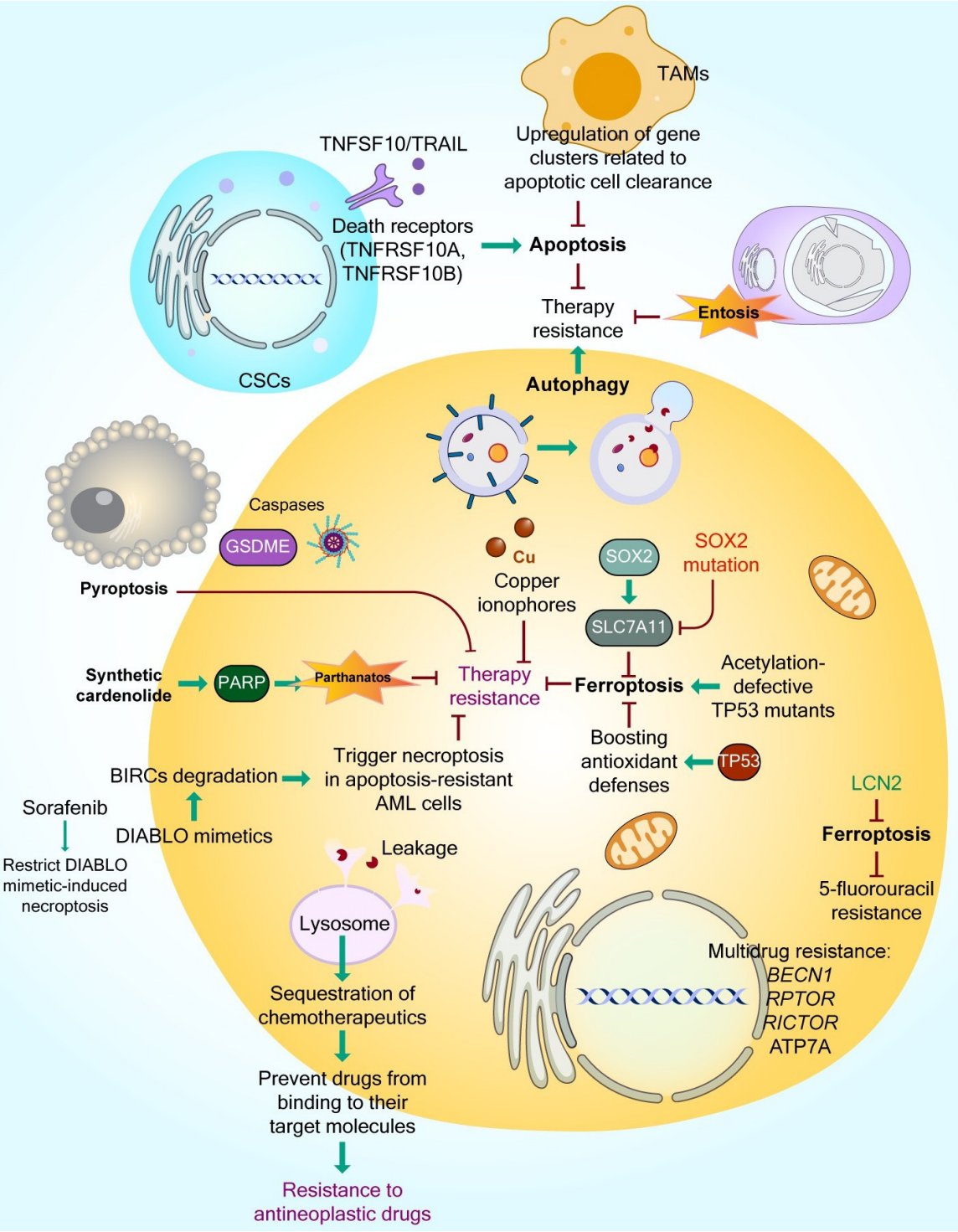


Figure 10. Interplay between regulated cell death, microenvironmental interactions, and therapeutic resistance in cancer. Therapy resistance is sustained by interconnected cytoprotective and death-evading programs, wherein enhanced autophagic flux promotes cell survival and entosis dampens anti-tumor efficacy, while tumor-associated macrophages (TAMs) upregulate apoptotic clearance genes to circumvent TNFSF10/TRAIL/death receptor (TNFRSF10A, TNFRSF10B)-mediated apoptosis in cancer stem cells (CSCs). Reactivation of distinct non-apoptotic cell death modes provides pathways to overcome resistance: caspase-dependent cleavage of GSDME induces pyroptosis, synthetic cardenolides activate PARP-driven parthanatos, and copper ionophores elevate intracellular copper levels to circumvent drug refractoriness. Additionally, DIABLO mimetics promote BIRC degradation to trigger necroptosis in apoptosis-resistant acute myeloid leukemia (AML) cells, a process antagonized by sorafenib. Ferroptotic cell death is modulated across multiple regulatory nodes: wild-type TP53 blunts ferroptosis by boosting antioxidant defenses, whereas acetylation-defective TP53 mutants promote ferroptotic susceptibility. Similarly, wild-type SOX2 upregulates the cystine/glutamate antiporter SLC7A11 to suppress ferroptosis, an effect reversed by loss-of-function SOX2 mutations, while LCN2 suppresses ferroptosis to drive 5-fluorouracil resistance. Furthermore, multidrug resistance is sustained transcriptionally by alterations in BECN1, RPTOR, RICTOR, and ATP7A, coupled with lysosomal sequestration and leakage-mediated compartmentalization of chemotherapeutic agents, preventing antineoplastic drugs from reaching their designated intracellular molecular targets.

Apoptosis

Although defects in apoptotic signaling are prevalent in cancer and have led to the development of therapies targeting this pathway, concerns remain about potential resistance to these therapies and unintended toxicity due to widespread apoptosis in healthy cells [14]. Cancer stem cells, which are known for initiating tumors and resisting therapy, often have reduced sensitivity to apoptosis [351-353]. Some CSCs express high levels of death receptors, increasing their susceptibility to TNFSF10/TRAIL-induced apoptosis; for example, SW480 colon cancer CSCs with elevated TNFRSF10A are more responsive to TNFSF10, and AT-3 mammary carcinoma CSC-like cells with high FAS and TNFRSF10B/DR5 levels show increased sensitivity to FASLG and TNFSF10 [354, 355].

BH3 mimetics, such as venetoclax (ABT-199), selectively inhibit BCL2 and have shown efficacy in chronic lymphocytic leukemia with minimal platelet toxicity [356, 357]. Broader-spectrum inhibitors targeting multiple BCL2 family proteins and IAPs are also in development, although concerns about off-target effects persist [358].

Senescent cancer cells, while halting proliferation, can evade apoptosis and contribute to relapse and resistance [359]. TNFSF10, which activates extrinsic apoptosis via TNFRSF10A and TNFRSF10B, is effective against senescent cells; a modified TNFSF10/TRAIL variant with preferential activity toward TNFRSF10B/DR5, induced stronger apoptotic responses in therapy-induced senescent cancer cells than wild-type TNFSF10/TRAIL [360].

Despite its therapeutic potential, apoptosis is a double-edged sword. High apoptosis rates are often observed in aggressive tumors and may promote genomic instability and tumor repopulation [13]. Apoptotic cells can also recruit macrophages and polarize them into M2-like states, which support tumor growth. However, tumor-associated macrophages can also suppress tumor expansion under certain conditions [361].

In a pivotal study, TAMs from “starry-sky” lymphoma showed gene expression profiles favoring apoptotic cell clearance, anti-inflammatory signaling, angiogenesis, and tissue repair, suggesting that phagocytosis of dying cells may enhance tumor-supportive features in the microenvironment [362]. These findings underscore the nuanced role of apoptosis in cancer and the importance of context-specific therapeutic strategies.

Among the agents that pharmacologically affect apoptosis, venetoclax (ABT-199) is a selective BCL2 inhibitor that is approved for CLL and AML patients and is dependent on BCL2 [357, 363]. It effectively triggers apoptosis, but resistance can arise via the upregulation of proteins such as MCL1, which often requires combination with cytotoxic or complementary apoptosis-inducing agents [363].

Venetoclax monotherapy has modest efficacy in AML patients who are unfit for intensive therapy (19% ORR) [364], suggesting the need for combination approaches. Adding venetoclax to HMAs yields substantially higher remission rates, including 61% CR/CRi in untreated elderly AML patients [365], strong activity across molecular subgroups with 10-day decitabine [366], and significantly improved OS and CR rates in VIALE-A patients (14.7 vs. 6.0 months; 36.7% vs. 17.9%) [367].

Compared with LDAC alone, venetoclax plus LDAC has favorable safety, a 54% CR/CRi rate, and an OS benefit, as confirmed in phase 3, with reduced mortality and superior responses [368]. Intensive regimens such as FLAG-Ida plus venetoclax achieve deep remission and improve post-HSCT outcomes [369]. Triplet therapy with venetoclax, decitabine, and an FLT3 inhibitor results in strong responses in patients with FLT3-mutated AML across treatment settings [370].

External apoptosis is triggered via TNF receptor superfamily death receptors (TNFSF10/TRAIL receptors TNFRSF10A and TNFRSF10B, FAS/CD95) [371]. Activators, including recombinant TNFSF10 and agonistic antibodies, stimulate DISC formation and CASP8 activation, which cascades to executioner caspases such as CASP3 [372, 373]. Clinical efficacy is often limited by resistance and toxicity to normal tissues, prompting research into improved delivery and combination strategies.

Overall, apoptosis-promoting agents restore the defective apoptotic machinery, with ongoing studies investigating the specificity, overcoming resistance, and enhancing safety of these agents.

Autophagy

The regulation of autophagy in the context of multidrug resistance has rapidly advanced in cancer research [374]. In an orthotopic mouse model, stable knockdown of the autophagy-related genes *Becn1* and *Atg5* in HCC cells effectively blocked lung metastasis. Interestingly, while autophagy suppression does not impair cell migration or invasion, it reduces resistance to cell death and hinders successful colonization of lung tissue [375].

In CRC, genes involved in autophagy, such as BECN1, RPTOR, and RICTOR, are associated with disease progression and multidrug resistance [376].

Studies examining oxidative stress and tumor metabolism have revealed a metabolic interplay between autophagy and aerobic glycolysis within the

tumor stroma. Cancer cells release hydrogen peroxide, which induces oxidative stress in surrounding fibroblasts. This stress activates autophagy, mitophagy, and glycolysis, reshaping the stromal environment to produce high-energy metabolites such as L-lactate. These nutrients are then utilized by cancer cells to fuel mitochondrial respiration. This metabolic crosstalk may offer new biomarkers and therapeutic targets [377].

Autophagy is increasingly recognized as a survival mechanism that shields cancer cells from apoptosis and contributes to chemotherapy resistance. Inhibiting autophagy has shown potential in sensitizing resistant tumors to anticancer drugs, supporting the strategy of combining autophagy inhibitors with cytotoxic agents [378]. Chloroquine (CQ) and hydroxychloroquine (HCQ), known autophagy inhibitors, have been realized to increase chemotherapy efficacy and overcome resistance in cancers [379, 380]. Cocco et al. found that CQ-mediated inhibition of autophagy could prevent resistance to PI3K and AKT inhibitors and augmented their antitumor effect in combination with paclitaxel in triple negative breast cancer models [381].

Further evidence suggests that silencing ATG14 and the oncogenic transcription factor FOXP1 in ovarian cancer cells increases their sensitivity to cisplatin. This effect is mediated by the overexpression of *MIR29C-3p*, which plays a key role in tumor progression [382].

With respect to controlling autophagic flux, autophagy recycles damaged organelles and proteins, with dual oncological roles in preventing early tumorigenesis or supporting established tumors. The lysosomotropic agents CQ and HCQ block autophagosome-lysosome fusion by increasing lysosomal pH, increasing the efficacy of cytotoxic and radiation therapy [383, 384]. The role of autophagy is context dependent: early tumor suppression involves reducing oxidative stress and genomic instability, whereas established tumors exploit autophagy for survival under stress [378, 385, 386].

Necroptosis

Cancer cells often evade necroptosis as a survival strategy. In many tumor types, key necroptotic regulators, such as RIPK3, are downregulated, allowing malignant cells to bypass this death pathway [387]. RIPK3 has been shown to suppress tumor growth, particularly in CRC, where its reduced expression is correlated with poorer survival outcomes [388].

Interestingly, sorafenib, a multikinase inhibitor used in AML therapy, interferes with DIABLO mimetic-induced necroptosis by blocking MLKL phosphorylation, thereby limiting cell death in resistant AML cells [389].

Cancer cells may also develop resistance to necroptosis-inducing agents. One mechanism involves adaptation to hypoxic conditions within the TME, which leads to increased reliance on anaerobic glycolysis. This metabolic shift helps neutralize mitochondrial reactive oxygen species via pyruvate, reducing susceptibility to RIPK1/RIP1- and RIPK3/RIP3-mediated necroptosis [142].

Complementary approaches, such as thermal therapy, antihypoxic treatments, or MLKL agonists combined with necroptosis-inducing agents, may further enhance therapeutic efficacy and overcome resistance [140].

Therapeutically, necroptosis can bypass drug resistance via the use of inhibitors targeting RIPK1, RIPK3, and MLKL [390, 391]. RIPK1 antagonists such as necrostatin-1 (Nec-1) prevent RIPK3 interaction [392]. RIPK3 inhibitors block MLKL activation, whereas MLKL antagonists such as necrosulfonamide inhibit membrane translocation [393].

Necroptosis enhances antitumor immunity via DAMP release, supporting immunotherapy combinations, although careful regulation is needed to avoid excessive inflammation or tumor-promoting effects [394]. Clinical translation requires patient selection and biomarker development for susceptibility.

Ferroptosis

Ferroptosis has emerged as a potential mechanism to counteract drug resistance. Ferroptosis susceptibility is influenced by factors other than RAS signaling that were initially linked to RAS-mutant cancers [395]. This pathway is gaining attention for its tumor-suppressive properties and its impact on cancer cell metabolism.

A study revealed that lung cancer stem-like cells resist ferroptosis through the overexpression of the cystine transporter SLC7A11, which is activated by the transcription factor SOX2. Mutation of the SOX2 binding site in the *SLC7A11* promoter decreases its expression and increases ferroptosis sensitivity. Tumors with high SOX2 levels are more resistant, and a positive correlation between SOX2 and SLC7A11 is observed in both mouse and human lung cancers. Therefore, targeting SOX2 oxidation may be a novel therapeutic approach [396].

The tumor suppressor TP53 plays a dual role in ferroptosis regulation. In some contexts, acetylation-deficient TP53 mutants can still suppress tumor growth via ferroptosis, even without inducing senescence or apoptosis [397]. In CRC, TP53 acts as a brake on ferroptosis triggered by erastin, and it does

so by curbing the enzymatic activity of dipeptidyl peptidase-4 (DPP4) through a route that does not require transcriptional regulation. When TP53 is lost, DPP4 is no longer sequestered in the nucleus and instead accumulates at the plasma membrane, where its activity drives peroxidation of membrane lipids, the terminal event that commits the cell to ferroptotic death [398].

Both preclinical and clinical studies have linked ferroptosis to treatment resistance. High-mesenchymal state cancer cells rely on GPX4 to avoid ferroptosis, and many chemotherapeutics can trigger this pathway. Disruption of ferroptosis signaling often leads to resistance [399, 400]. Moreover, metastatic cells tend to be resistant to ferroptosis, and silencing GPX4 reduces their tumorigenic and metastatic potential [401, 402].

Tumor cells, whether inherently resistant or acquired resistant, often increase their antioxidant defenses to suppress ferroptosis, enabling survival under therapeutic stress. Inducing ferroptosis may reverse this resistance and improve responses to chemotherapy, targeted therapy, and immunotherapy [400]. Recent research has also revealed the role of ferroptosis in immune responses. Jiang et al. reported that the suppression of ferroptosis contributes to resistance to anti-PDCD1-CD274/PD-L1 therapies, suggesting that activating ferroptosis could be key to overcoming immunotherapy resistance [403].

From a therapeutic perspective, ferroptosis induction is promising for drug-resistant tumors [404]. RSL3 has been found to trigger ferroptosis by inactivating GPX4 and ROS generation in CRC [405]. LCN2 (lipocalin 2), which regulates iron metabolism, is elevated in several cancers and contributes to 5-fluorouracil resistance by inhibiting ferroptosis [406].

Iron chelators (e.g., deferoxamine and deferiprone) reduce free iron, modulating ferroptosis, and protecting normal cells [407]. Combining ferroptosis inducers with anti-cancer therapies, particularly immunotherapy, enhances tumor killing [408, 409]. Biomarker-guided delivery systems (e.g., nanoparticles and conjugates) optimize safety and potency [410-412]. Overcoming resistance requires targeting multiple ferroptosis-associated pathways [400].

Pyroptosis

Recent studies have revealed a strong link between pyroptosis and both the onset and spread of various cancers [413-416]. Pyroptosis has the capacity to activate interactions between the innate and adaptive branches of the immune system, reshaping the TME to promote immune activation. This immune-stimulating shift enhances tumor infiltration and supports metastatic progression [285, 417, 418]. Moreover, treatment regimens combining BRAF and MAP2K inhibitors induce pyroptosis, thereby altering the TME [419].

In many cancer cell lines, resistance to chemotherapy arises from defects in apoptotic pathways, making pyroptosis a promising alternative for therapeutic intervention [420]. Pyroptosis also plays a critical role in increasing the efficacy of immunotherapies; for instance, a recent pan-cancer study mapped GSDSM expression across tumor types and linked it to key immune readouts. The standout result was widespread GSDMD overexpression, seen in gastric, colon adenocarcinoma, and breast cancers, which tracked with greater abundance of tumor-infiltrating $CD8^+$ T cells, M1 macrophages, and NK cells, a pattern of potential benefit. By contrast, GSDMB correlated negatively with these parameters in breast cancer [421, 422].

However, compared with normal cells, most tumor cells exhibit reduced GSDME expression, largely due to the methylation of GSDME mRNA [423]. This downregulation limits pyroptosis activation. Therefore, selecting chemotherapeutic agents on the basis of GSDME expression levels may improve treatment outcomes. Increasing GSDME levels in tumor cells can increase their sensitivity to chemotherapy and reduce drug resistance [211].

A recent discovery revealed a pyroptosis-related gene (PRG) signature, including CASP4, CASP9, GSDMC, and IL1A, that enables the classification of glioma patients into high- and low-risk groups. This PRG profile not only aids in diagnosis and prognosis but also provides insights into immune cell infiltration and TME dynamics, offering potential guidance for immunotherapy strategies [424].

Pyroptosis can be triggered by inflammatory caspases (incl. CASP1, CASP4, CASP5, and CASP11) to promote tumor cell death and immune activation [417]. Combining pyroptosis inducers with immunotherapy enhances antitumor efficacy. Precision delivery and prodrug designs improve specificity and safety [420].

CASP1 or CASP4, CASP5 and CASP11 activators induce tumor pyroptosis, releasing cytokines that recruit and activate immune cells, converting the TME to a more immunogenic state [425, 426].

Factors such as DAMPs can enhance pyroptosis activity, resulting in dendritic cell maturation and T-cell responses [417]. Synergistic combinations include immune checkpoint inhibitors and adoptive cell therapies, increasing tumor immunogenicity and therapeutic effectiveness [427, 428]. Targeted delivery and prodrug approaches minimize systemic toxicity, transforming immunologically "cold" tumors into

"hot" tumors responsive to immunotherapy [429, 430].

Cuproptosis

Copper ionophores, including elesclomol/ES, are being evaluated in clinical settings for their ability to manipulate intracellular copper and iron levels, aiming to overcome chemotherapy resistance [431, 432]. Disulfiram/DSF, an FDA-approved redox-active molecule, has been demonstrated to enhance the effects of radiation and chemotherapy in NSCLC, particularly under hypoxic conditions. It improves the therapeutic impact of carboplatin and radiation in xenograft models [433]. Additionally, ATP7A, as a key copper transporter, has been found to be associated with tumor immune infiltration and immune checkpoint function in HCC, suggesting its role as a predictive biomarker for immunotherapy and targeted therapy in this malignancy [434]. Despite their promise, copper ionophores often act through multiple pathways, and their specific role in cuproptosis remains underexplored.

Parthanatos

PARP1 plays a vital role in maintaining genomic integrity and orchestrating DNA repair mechanisms. Currently, several clinical trials are investigating PARP inhibition, and several agents, such as niraparib, rucaparib, talazoparib, and olaparib, have received FDA approval [435].

AIFM1/AIF, a key downstream effector of PARP1-mediated cell death, is crucial for the assembly of mitochondrial respiratory complex I and energy production. Experimental models using orthotopically implanted tumors in immunodeficient mice revealed that reduced AIFM1 levels promote EMT, facilitating metastasis. This is partly due to oxidative suppression of the tumor suppressor PTEN [436], which also contributes to drug resistance in NSCLC [437]. Therapeutic strategies aimed at modulating AIFM1 have been explored, with evidence suggesting that AIFM1 activation may be correlated with chemotherapy outcomes in patients with triple negative breast cancer [438].

Interestingly, a synthetic cardenolide, which is structurally similar to digitoxin and digoxin, was found to induce parthanatos by upregulating PARP and poly(ADP-ribose)/PAR in drug-resistant cancer cells overexpressing ABC transporters such as ABCB1 and ABCB5. Notably, this effect occurred independently of ROS [439].

Lysosome-dependent cell death

Lysosomes contribute to chemotherapy resistance by sequestering drugs, preventing them from reaching their intended intracellular targets [440]. Agents such as doxorubicin and TKIs accumulate in lysosomes and stimulate lysosomal biogenesis, further enhancing drug sequestration [441]. Additionally, lysosomal drug buildup can trigger exocytosis, releasing contents outside the cell and reducing drug efficacy through a mechanism distinct from ABC transporter-mediated efflux [441, 442].

Entosis

Entosis, a form of cell-in-cell death, has been observed in multiple cancers and is considered a tumor-suppressive process with potential relevance to therapy resistance [443]. While its exact role remains under investigation, entosis is emerging as a prognostic marker, and compounds that induce entosis are being explored as anticancer agents [444].

However, high levels of entotic structures in tumors have also been linked to disease progression. Clinical studies in head and neck squamous cell carcinoma, lung adenocarcinoma, and pancreatic ductal adenocarcinoma (PDAC) have shown correlations between entosis and poor prognosis or recurrence [444]. The internalized cells within the entotic vacuoles may be shielded from chemotherapy, and their eventual release could lead to treatment failure [247].

In prostate cancer, entosis has been identified as a survival strategy against the TKI nintedanib [445]. This process is particularly relevant in PDAC liver metastases, where the *NET1* gene, which is closely related to entosis, is upregulated. *NET1* expression is correlated with aggressive tumor behavior and poor outcomes, suggesting that entosis-driven NET1 activation contributes to PDAC progression [446].

CLINICAL TRANSLATIONS

While therapies that activate RCD pathways offer significant potential in oncology, the development of resistance remains a major clinical challenge [464]. This section explores how cancer cells evade cell death-inducing treatments and outlines strategies to counteract this resistance (**Table 3**). Since therapeutic tolerance is a central obstacle [464], understanding the underlying biological mechanisms is essential for designing effective interventions. Promising approaches include combination regimens, antiapoptotic protein targeting, epigenetic reprogramming, autophagy inhibition, immune system enhancement, and personalized medicine strategies, all aimed at improving treatment outcomes [465-471]. Ongoing research and clinical trials continue to refine these methods and expand the arsenal against resistant cancers.

Table 2. Therapeutic Targets and Regulation of Major Cell Death Pathways in Cancer

TARGET CELL DEATH PATHWAY	THERAPEUTIC STRATEGY/MODULATION	REPRESENTATIVE AGENTS OR TARGETS	MECHANISTIC OR CLINICAL INSIGHTS	REFERENCE(S)
Apoptosis	Targeting anti-apoptotic BCL2 family proteins (intrinsic pathway)	Venetoclax (ABT-199), Navitoclax (ABT-263), BH3 mimetics	Venetoclax selectively inhibits BCL2 to restore apoptosis in CLL and AML; combination strategies aim to overcome resistance mediated by MCL1 upregulation.	[356, 447-449]
	Activating death receptor signaling (extrinsic pathway)	Recombinant TNFSF10/TRAIL, agonistic antibodies against TNFRSF10A, TNFRSF10AB and FASLG	TNFSF10-TNFRSF10A-TNFRSF10B interaction forms DISC and activates CASP8, inducing apoptosis; clinical limitations due to resistance and toxicity in normal cells.	[371, 372, 450, 451]
Autophagy	Inhibiting lysosomal fusion and degradation to block pro-survival autophagy	Chloroquine (CQ), hydroxychloroquine (HCQ)	CQ, HCQ elevate lysosomal pH and inhibit autophagosome-lysosome fusion; enhance chemosensitivity but require monitoring due to retinal toxicity.	[452-454]
Necroptosis	Blocking necroptotic mediators to control inflammation or modulate immune response	Necrostatin-1 (Nec-1), GSK2982772 (RIPK1 inhibitor), GSK-872 (RIPK3 inhibitor)	RIPK1 and RIPK3 inhibition prevents necroptosis-related tissue injury; necroptosis induction proposed as an alternative in apoptosis-resistant cancers; potential synergy with immunotherapy.	[141, 279, 455, 456]
Ferroptosis	Inhibiting GPX4 to induce iron-dependent lipid peroxidation	RSL3, ML210	GPX4 inhibition increases ROS and lipid peroxide accumulation, leading to ferroptosis in Ras-driven and drug-resistant cancers.	[457-460]
	Combination therapies integrating ferroptosis and other modalities	GPX4 inhibitors + ROS inducers or immune checkpoint blockade	Cotargeting oxidative and immune pathways enhances anti-tumor efficacy and overcomes ferroptosis resistance; precision delivery systems under development.	[409, 461, 462]
Pyroptosis	Activating inflammatory caspases to induce immunogenic death	CASP activators; GSDMD agonists	Caspase activation leads to pore formation, cytokine release, and immune stimulation; promising for apoptosis-resistant tumors.	[417, 426, 463]

Resistance to cell death-inducing treatments often stems from genetic mutations and altered cellular signaling: mutations in BCL2 family proteins such as BAX and BAK1 can prevent mitochondrial membrane permeabilization, a key step in apoptosis [472]; TP53 mutations impair the ability of cells to initiate apoptosis in response to DNA damage and stress signals [91, 102, 473]; overexpression of antiapoptotic proteins such as BCL2, BCL2L1/BCL-XL, and MCL1 can sequester proapoptotic factors, blocking apoptosis and reducing sensitivity to BCL2 inhibitors such as venetoclax [474-476].

Cancer cells also upregulate autophagy in response to stress, including exposure to cell death-inducing agents, enabling survival through cytoprotective autophagy [477].

Epigenetic modifications, such as DNA methylation and histone changes, can silence genes involved in apoptosis, pyroptosis, and ferroptosis further promoting resistance [478-481].

Combination therapies offer a powerful means to enhance efficacy and bypass resistance mechanisms in cancer treatment [482, 483]. Dual-targeting strategies, such as combining BCL2 inhibitors with PI3K inhibitors, can prevent the activation of compensatory survival pathways; moreover, coadministering BCL2 and MCL1 inhibitors addresses multiple nodes in the apoptotic network, effectively restoring cell death. The development of selective MCL1 inhibitors and dual-targeting agents may further overcome resistance [484, 485]. Epigenetic therapies, including DNA methylation inhibitors and histone deacetylase inhibitors, can reactivate silenced proapoptotic genes and promote cell death [486-488].

Enhancing immune responses through immunotherapy, such as combining cell death-targeted treatments with checkpoint inhibitors, can help eliminate resistant cancer cells via immune-mediated mechanisms [489]. Cancer vaccines and adoptive T-cell therapies targeting antigens released during cell death may further strengthen immune responses [490-494]. Precision medicine approaches, including biomarker-driven therapy and comprehensive genomic profiling, also enable the identification of resistance markers and guide the selection of optimal combination strategies tailored to individual patients [495].

Integrating cell death-inducing agents with conventional treatments such as chemotherapy and immunotherapy has shown promise in enhancing therapeutic efficacy and overcoming resistance [25, 496].

Chemotherapeutic agents typically induce cell death by damaging DNA, disrupting replication, or halting cell division. When paired with cell death-targeting drugs, this dual approach can intensify

apoptosis. For example, combining venetoclax with cytarabine has demonstrated increased effectiveness in AML [369]. Similarly, PARP inhibitors, which impair DNA repair, can be used alongside DNA-damaging chemotherapy to increase cell death in BRCA-mutated cancers [497, 498].

Table 3. Major findings on targeting and regulation of cell death pathways in therapeutic resistance

MECHANISM	THERAPEUTIC TARGET OR APPROACH	MECHANISTIC INSIGHT/REGULATORY FOCUS	REPRESENTATIVE AGENT(S)	THERAPEUTIC IMPLICATION	REFERENCE(S)
Apoptosis	TP53	Mutations or altered expression disrupt mitochondrial permeabilization and apoptotic signaling	Venetoclax resistance	Disrupts MYC transcriptional program and overcomes venetoclax resistance in acute myeloid leukemias	[474, 507]
	MCL1 and BCL2	Combination Therapy (Preclinical models and a Phase Ib study)	Polatuzumab vedotin and venetoclax	Targeting MCL1 and BCL2 with polatuzumab vedotin and venetoclax overcomes treatment resistance in R/R non-Hodgkin lymphoma	[484]
Cytoprotective and Lysosomal Autophagy	Autophagy-related genes, LC3, and BECN1	Stress-induced autophagy allows survival during treatment	Chloroquine, hydroxychloroquine	Blocking autophagy enhances cytotoxicity of chemo- and radiotherapy	[477, 508]
Epigenetic Reprogramming	m6 methylation, histone acetylation/deacetylation	Silencing of cell death	HDACis, m6 methylating chemo-drugs	Reactivates pro-death genes and sensitizes tumors to therapy	[486, 509]
Chemotherapy Integration	DNA damage and replication arrest	Cytotoxic synergy enhances apoptotic cascade	Venetoclax + cytarabine PARP inhibitors + DNA-damaging agents	Improved response in AML and BRCA-mutant cancers	[369, 498]

As we know, immune checkpoint inhibitors (e.g., anti-PDCD1 and anti-CTLA4) enhance the ability of the immune system to recognize and destroy cancer cells [499, 500]. Furthermore, cell death-targeted therapies can increase the release of tumor antigens, increasing immune activation [25, 501]. Thereby, combining these therapies can intensify immune-mediated tumor clearance [502, 503]. Additionally, pairing cell death-inducing agents with adoptive T-cell therapies can improve antigen presentation and enhance T-cell-mediated cytotoxicity [504-506].

LIMITATIONS AND CHALLENGES

The integration of multiple therapeutic approaches has become a strategic method to increase the effectiveness of cancer treatments. These combinations often produce synergistic effects, where the collective impact exceeds the sum of individual therapies [510, 511]. This strategy helps overcome resistance by simultaneously targeting several survival pathways [510]. Utilizing combination regimens may also allow for lower dosages of each drug, thereby minimizing overall toxicity and reducing side effects commonly associated with high-dose monotherapy [512]. Moreover, such approaches can more effectively address tumor heterogeneity by targeting distinct subpopulations of cancer cells within the tumor mass [513]. Treatments that induce cell death can also increase the release of tumor antigens, increasing the efficacy of immunotherapies and stimulating a stronger immune response [514].

Despite their potential, combination therapies also present several complex challenges:

i. Determining the most effective sequence, timing, and dosage of combined therapies to maximize synergy while minimizing toxicity is a complex task [515-517].

ii. Combining multiple therapeutic agents can increase the likelihood of adverse effects, cumulative toxicities, and unexpected pharmacological interactions, necessitating close monitoring and careful management of patient health [518, 519].

iii. The development of reliable biomarkers to predict which patients will benefit from specific therapeutic combinations remains a critical yet demanding endeavor [427, 520]. This requires extensive research and clinical validation.

iv. Even with combination strategies, tumors can evolve new resistance mechanisms [3]; continuous research is essential to understand and counteract these adaptive responses. Tumor plasticity, clonal evolution, and dynamic changes within the tumor microenvironment may enable cancer cells to adapt to simultaneous therapeutic pressures, ultimately reducing long-term treatment efficacy [521, 522].

v. The financial burden associated with multiagent therapies can be substantial, creating barriers for both healthcare systems and patients [523]; this challenge is further amplified when advanced nanotechnology-based delivery systems, personalized treatment approaches, or sophisticated biomarker-guided therapies are incorporated. Ensuring equitable access to these innovative treatments, particularly in low-resource settings, remains a pressing concern.

OUTLOOK AND PERSPECTIVES

Cancer treatment is undergoing rapid transformation, driven by breakthroughs in understanding cell death mechanisms, advanced drug delivery technologies, and personalized therapeutic strategies [524]. Herein, we outline key forward-looking directions and research opportunities that hold promise for improving clinical outcomes in oncology.

Technologies such as high-throughput screening (HTS) and multi-omics platforms are accelerating progress in identifying new therapeutic targets [525]. HTS enables the rapid assessment of thousands of chemical compounds or genetic alterations, facilitating the discovery of agents that can modulate cellular processes such as cell death [526]. HTS applications include screening small molecules and RNA interference (RNAi) tools to uncover novel pathways and targets involved in RCD [527]. For instance, identifying compounds that selectively induce cell death, such as apoptosis, in cancer cells, while sparing healthy tissue can lead to safer and more effective treatments [526, 528].

Omics approaches, encompassing genomics, proteomics, and metabolomics, play a complementary role. Genomic tools such as whole-genome sequencing and transcriptomics reveal mutations and expression changes linked to the regulation of cell death. Proteomics, which uses mass spectrometry, identifies shifts in protein levels, modifications, and interactions within death-related pathways. Metabolomics uncovers metabolic shifts that influence cell death, offering insights into vulnerabilities in cancer metabolism. Integrating these datasets provides a comprehensive view of cell death dynamics and helps pinpoint actionable therapeutic targets [529-531].

Biomarkers are essential for guiding treatment decisions and improving patient outcomes [532]; these kinds of biomarkers are principally categorized into predictive biomarkers that help identify patients likely to benefit from specific therapies, and prognostic biomarkers that offer insights into disease trajectory and help stratify patients by risk, informing treatment intensity [532]. For example, Apoptosis- and autophagy-associated markers can predict survival in patients with neoadjuvant treated esophageal adenocarcinoma [533], and dynamic biomarker assessment can shape therapeutic decisions in HR-positive/ERBB2/HER2-negative breast cancer. Approaches range from tissue and liquid biopsies to metabolic imaging and microbiome profiling, all of which track tumor- or host-derived shifts as they unfold over time [534].

Nanoparticle-based delivery systems offer significant advantages by improving drug accumulation in tumors and minimizing systemic side effects [535, 536]. Liposomal formulations, such as liposomal doxorubicin in breast cancer, increase the drug concentration at the tumor site while reducing toxicity elsewhere [537, 538].

Targeted delivery methods use ligands, antibodies, or peptides to direct drugs specifically to cancer cells. ADCs, which link monoclonal antibodies to cytotoxic agents, exemplify this approach by ensuring selective delivery to tumor cells expressing specific antigens [539, 540].

The TME, characterized by hypoxia, a dense ECM, and aberrant vasculature, presents substantial barriers to effective drug delivery [541]. Strategies to modify the TME, such as the use of agents that normalize blood vessels or degrade ECM components, can improve drug penetration; for instance, combining VEGF inhibitors with chemotherapy enhances vascular function and drug delivery [542]. Resistance mechanisms such as drug efflux and metabolic degradation also reduce drug efficacy; solutions include codelivery of efflux pump inhibitors that ensure selective activation within the tumor [543].

In addition to molecular profiling, personalized oncology will increasingly incorporate patient heterogeneity, including epigenetic characteristics, immune status, metabolic signatures, comorbidities, lifestyle factors, treatment preferences, and psychosocial determinants of health [471, 495]. Integrating these multidimensional datasets through artificial intelligence and systems biology approaches may improve patient stratification, optimize therapeutic selection, and support truly individualized cancer care.

In summary, the future of cancer therapy lies in integrating HTS and omics technologies for target discovery, advanced drug delivery platforms for precise therapeutic delivery, and personalized medicine approaches tailored to each patient's biological and clinical characteristics. Discovering new cell death regulators and developing robust biomarkers will enable more targeted interventions. Advances in nanotechnology and targeted delivery systems will help overcome current limitations and enhance therapeutic impact, whereas personalized therapeutic strategies promise improved efficacy and reduced toxicity through individualized treatment selection. Continued innovation and interdisciplinary research are essential to fully realize these strategies in clinical practice.

Despite these advances, several practical challenges remain. High costs and technological complexity can limit accessibility and scalability, especially in resource-limited settings. Patient

variability in treatment response complicates personalization and prediction. Limitations in modeling complex biological systems may lead to unexpected outcomes and reduced effectiveness. Additionally, ethical and regulatory concerns surrounding genetically engineered therapies and potential off-target effects must be addressed to ensure safe and equitable implementation. These challenges underscore the need for ongoing research, technological refinement, and policy development to support the responsible integration of emerging cancer therapies.

Conclusion and remarks

The complex control of RCD serves as a vital factor in determining the success of cancer interventions. The capacity of cancer cells to evade apoptotic and nonapoptotic death processes is the core of the ongoing issue of drug resistance, tumor reemergence, and spread. Progress in clarifying the molecular foundations of RCD, encompassing the equilibrium between pro- and antiapoptotic elements, alternative forms of cell death, and their connections to inflammation and immune reactions, presents encouraging opportunities for therapeutic action. Addressing elements of these routes together with tolerance processes such as autophagy, necroptosis, and efflux carriers delivers a multidimensional tactic to heighten tumor vulnerability and prevent intervention shortcomings. Prospective translational studies focused on accurately adjusting RCD and surmounting tumor diversity will prove essential in refining anticancer interventions. This thorough insight promotes the development of advanced therapeutics that could markedly improve patients' ability to combat tolerant cancers.

Abbreviations

ABC: ATP-binding cassette; ADR: adriamycin; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; AMPK: AMP-activated protein kinase; BCSCs: breast cancer stem cells; CIN: chromosome instability; CLL: chronic lymphocytic leukemia; CQ: chloroquine; CRC: colorectal cancer; CS: chromosomal instability score; CSCs: cancer stem cells; ctDNA: circulating tumor DNA; CTLs: cytotoxic T lymphocytes; DAMPs: danger/damage-associated molecular patterns; DCs: dendritic cells; DISC: death-inducing signaling complex; ECM: extracellular matrix; EMT: epithelial-mesenchymal transition; EOC: epithelial ovarian cancer; ER: endoplasmic reticulum; HCC: hepatocellular carcinoma; HCQ: hydroxychloroquine; HGSOC: high-grade serous ovarian carcinoma; NSCLC: non-small cell lung cancer; HTS: high-throughput screening; IAPs: inhibitors of apoptosis; ICD: immunogenic cell death; ITH: intratumor heterogeneity; LCD: lysosome-dependent cell death; LMP: lysosomal membrane permeabilization; lncRNA: long noncoding RNA; LPS: lipopolysaccharide; MUFA: monounsaturated fatty acid; NBD: nucleotide-binding domain; NK: natural killer; NSCLC: non-small cell lung cancer; PCD: programmed cell death; PDAC: pancreatic ductal adenocarcinoma; PI3K: class I phosphoinositide 3-kinase.

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Conceptualization: OV, KH, and APK. Literature search & Data collection: OV, DJK, JR, MA, WJO, RJR, WCC, KSA, and KH. Writing-original draft: OV, DJK, JR, MA, WJO, RJR, WCC, KSA, and KH. Writing-review & editing: OV, DJK, JR, MA, WJO, RJR, WCC, KSA, KH, and APK. Supervision & Project administration: KH and APK. All the authors read and approved the final manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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