ISSN 0006-2979, Biochemistry (Moscow), 2026, Vol. 91, No. 10, pp. 1731-1755 © Pleiades Publishing, Ltd., 2026.

REVIEW

The Dual Role of Cell Death in Cancer Pathogenesis and Antitumor Therapy: From Linear Models to Integrative Representations

Ekaterina Sh. Kuligina[1], Grigoriy A. Yanus[1,2], and Evgeny N. Imyanitov[1,2,a]*

[1]*Petrov National Medical Research Center of Oncology, Ministry of Health of the Russian Federation, 197758 St. Petersburg, Russia*

[2]*St. Petersburg State Pediatric Medical University, Ministry of Health of the Russian Federation, 194100 St. Petersburg, Russia*

[a]*e-mail: evgeny@imyanitov.spb.ru*

Received September 4, 2026
Revised September 29, 2026
Accepted September 29, 2026

Abstract—Regulated cell death (RCD) is a central mechanism for maintaining tissue homeostasis. Dysregulation of RCD plays a key role in the emergence of transformed clones, tumor progression, the development of drug resistance, and the interaction of tumor cells with their microenvironment. Over the past several years, the conceptual framework of RCD has undergone substantial revision. Rather than viewing apoptosis as a predominant form of programmed cell death, current evidence supports a complex network of interconnected and partially redundant RCD pathways, including apoptosis, necroptosis, autophagy, pyroptosis, ferroptosis, cuproptosis, and others. This review summarizes current knowledge of the molecular mechanisms and the role of major forms of RCD in carcinogenesis, focusing on the classical "big three" (apoptosis, necroptosis, and autophagy), as well as pyroptosis and ferroptosis, which have received increasing attention in recent years. We discuss molecular triggers and signaling pathways that determine the choice of cell death programs and examine how genetic, metabolic, and immunological factors regulate the transition between alternative RCD modalities. Particular emphasis is placed on the context-dependent dual role of RCD in cancer: although RCD can eliminate transformed cells, certain forms of cell death may also sustain chronic inflammation, remodel the tumor microenvironment, facilitate therapeutic resistance, and contribute to immune evasion. Increasing evidence suggests that further advances in anticancer treatment may require a shift from the selective activation of individual cell death pathways toward context-dependent modulation of the integrated RCD network. Such strategies should account for tumor-specific biology, intratumoral heterogeneity, and the dynamic tumor microenvironment. The review examines current approaches to the pharmacological modulation of RCD and evaluates the efficacy of antitumor agents both as monotherapies and in combination with targeted therapies, chemotherapy, and immunotherapy. These advances may provide a foundation for therapeutic strategies designed to eliminate even highly adaptive tumor subpopulations that are capable of surviving therapeutic stress, including persister, circulating, and cancer stem cells.

DOI: 10.1134/S0006297926603096

Keywords: regulated cell death, programmed cell death, cancer biology, neoplasm, antitumor therapy, apoptosis, necroptosis, PANoptosis, autophagy, pyroptosis, ferroptosis

INTRODUCTION

Regulated cell death (RCD) is essential for maintaining tissue homeostasis and structural integrity of tissues. Although several million cells die every second in a healthy adult human body, excessive cell death contributes to a wide range of pathological conditions, such as acute myocardial infarction, stroke, chronic obstructive pulmonary disease, acute renal failure, Alzheimer's disease, and other neurodegenerative

* To whom correspondence should be addressed.

disorders [1, 2]. At the same time, insufficient cell death is a critical feature of neoplastic transformation and tumor progression, as it promotes the survival and accumulation of transformed cells carrying DNA damage, weakens negative selection during tumor clonal evolution, facilitates evasion of immune surveillance, and contributes to the development of therapeutic resistance [3, 4]. However, excessive or persistent activation of cell death pathways can also exert tumor-promoting effects, which may result from the release of mitogenic signals and growth factors into the tumor microenvironment through apoptosis-induced compensatory proliferation, the production of pro-inflammatory cytokines, and the depletion of effector cells involved in antitumor immunity [5-7].

Thus, although targeting cell-death pathways represents an attractive strategy for anticancer therapy, the dual and context-dependent roles of these molecular processes in the tumor microenvironment ecosystem necessitate careful consideration for their potential unintended consequences [8, 9].

The challenges associated with elucidating clinically relevant aspects of RCD are further compounded by the rapid expansion of knowledge regarding diverse mechanisms governing its initiation, execution, and regulation [10]. A specific mode of cell death is determined largely by the nature of initiating signals, which may include (i) exogenous stimuli, such as conserved molecular structures derived from microorganisms, known as pathogen-associated molecular patterns (PAMPs), and (ii) endogenous signals generated in response to cellular damage (e.g., radiation and toxins), as well as disturbances in intracellular metabolism, DNA repair, or replicative processes, collectively referred to as damage-associated molecular patterns (DAMPs) [11, 12]. Notably, the same signals may trigger different cell death programs depending on the tumor genetic context, the metabolic state of the cell, and the nature of its interactions with the immune system [13, 14]. Accordingly, RCD is now increasingly viewed not as a collection of independent signaling cascades, but as a complex and dynamic network of interconnected and often partially redundant programs that contribute to tissue homeostasis while integrating carcinogenesis, inflammation, regeneration, immune surveillance, and responses to therapeutic stress within a unified functional system [11, 15].

This article provides an up-to-date overview of the major RCD forms, highlighting the paradigm shift from the traditional “linear” model of programmed cell death toward a network-based and context-dependent framework. We further discuss how this conceptual transformation is shaping the development of novel therapeutic strategies for cancer, particularly those aimed at selectively modulating key components of RCD pathways.

EVOLUTION OF RCD CONCEPTS: SYSTEMATIZATION OF DIVERSITY AND TRANSITION FROM A LINEAR MODEL TO AN INTEGRATIVE NETWORK CONCEPT

Until relatively recently, cell death had been thought to occur through two fundamentally distinct scenarios: an unregulated process driven by nonspecific and catastrophically adverse external conditions, namely necrosis, or a precisely orchestrated sequence of events initiated by specific internal or external stimuli that was termed apoptosis, or programmed cell death [16]. Over the past quarter-century, however, a wide range of processes leading to cell death have been identified. More than 20 forms of RCD are now recognized, including necroptosis, pyroptosis, ferroptosis, paraptosis, parthanatos, entosis, NETosis, cuproptosis, oxeiptosis, disulfidptosis, and PANoptosis, among others [10, 17]. Four additional processes were described in 2025 alone that have been proposed as distinct forms of RCD: necrosis by Na^+ overload, FLOATosis (fused lysosome-associated termination), mitoxyperilysis, and spectosis, which is triggered by the complement system activation [10]. In some cases, the term refers not to a distinct cell death mechanism but rather to a particular physiological or pathological context that induces it. Anoikis, for example, is an apoptotic response that normally prevents the growth of epithelial cells in the absence of integrin-mediated attachment to the extracellular matrix [18]. Similarly, specific disturbances in cellular homeostasis can activate distinct forms of RCD. Disturbances in redox balance, lipid homeostasis, and iron metabolism can lead to ferroptosis, oxeiptosis, and oxytosis [19]. Mitochondrial copper imbalance induces cuproptosis [20], whereas impaired cysteine metabolism can trigger disulfidptosis. Disruption of pH homeostasis promotes alkaliptosis [21], while defects in DNA repair can activate PARP1 (poly[ADP-ribose] polymerase 1)-mediated parthanatos [22]. Dysregulation of lysosomal zinc homeostasis induces lysosome-mediated zinc-dependent cell death (lysozincrosis) [23].

It should be noted that the latest consensus guidelines for the classification of cell death modalities, developed by the Nomenclature Committee on Cell Death (NCCD), were published in 2018 and therefore do not fully capture the rapidly evolving body of research in this field [17]. Since then, the remarkable biological diversity of cell death pathways has become increasingly evident. These pathways differ in their effects on the microenvironment of dying cells, including their immunogenicity, the extent to which they expose or release antigenic material, and the degree of local inflammation associated with RCD. These mechanisms also differ in the stimuli and cellular conditions that trigger specific RCD modalities,

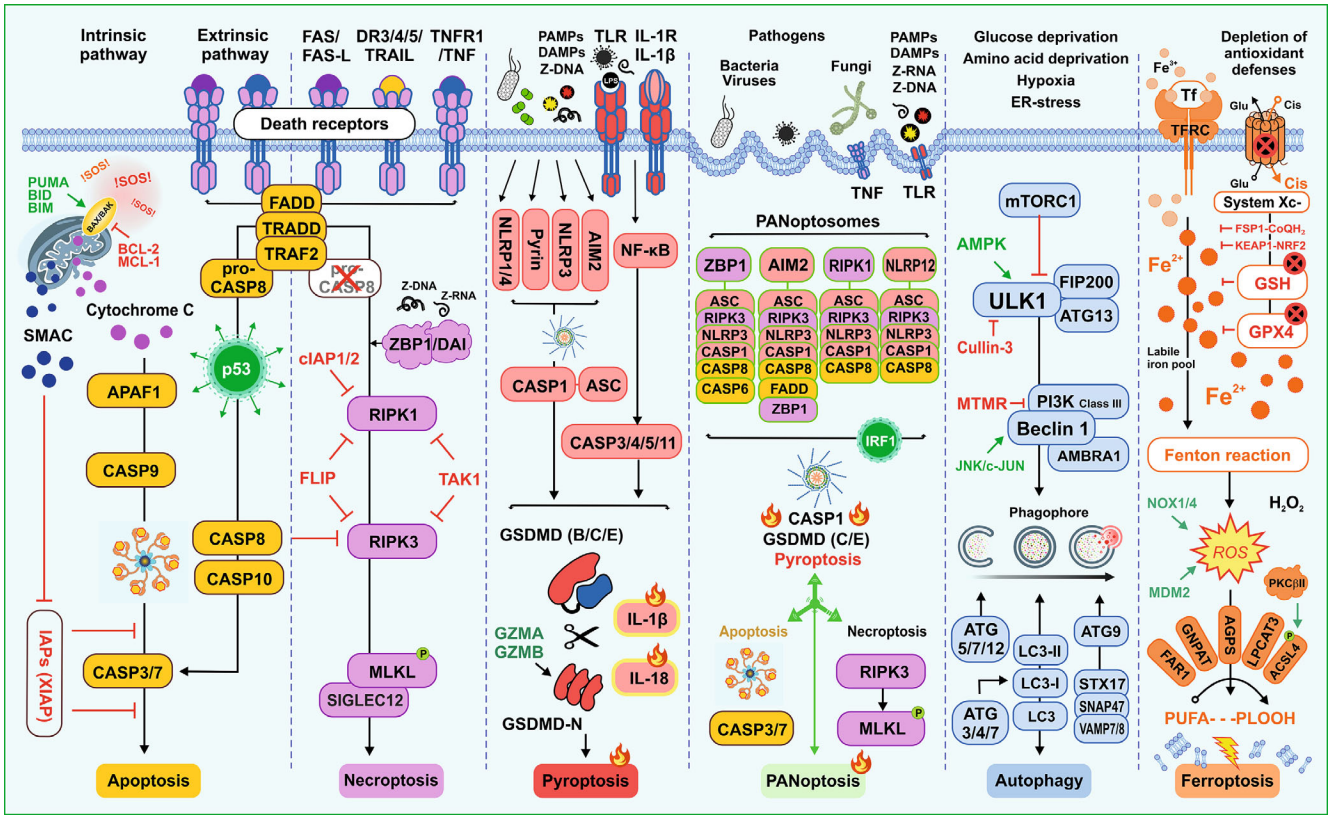

Fig. 1. RCD pathways: apoptosis, necroptosis, pyroptosis, PANoptosis, autophagy, and ferroptosis.

influence the kinetics of their progression, or prevent the process from reaching completion [11]. Importantly, RCD pathways are not independent of one another. Instead, they are interconnected through multiple regulatory nodes at which distinct features of the cellular state can determine whether cell death proceeds through one pathway or another or, alternatively, whether the process of dying is suspended (Fig. 1).

APOPTOSIS AND APOPTOSIS-LIKE CELL DEATH: CLASSICAL MECHANISMS AND ATYPICAL VARIANTS

Apoptosis is the most extensively studied form of RCD and is characterized by a set of conserved morphological features, including a reduction in cell volume, chromatin condensation and DNA fragmentation, and preservation of the plasma membrane integrity until the formation of apoptotic bodies. Apoptotic bodies are subsequently cleared through efferocytosis (uptake by macrophages), typically without eliciting a pronounced inflammatory response [24].

The intrinsic pathway of apoptosis and apoptosis-like cell death. The intrinsic apoptotic pathway can be activated by a remarkably broad range of stimuli, including metabolic and proteotoxic stresses, hypoxia, DNA damage, and growth factor deprivation (Fig. 1; Table S1 in Online Resource 1). Its central regulators are members of the Bcl-2 protein family of antiapoptotic proteins (BCL-2, BCL-XL, BCL2L10/BOO/DIVA, and MCL-1), proapoptotic, stress-inducible BH3-only proteins (BAD, BIM, BMF, BIK, HRK/DP5, BFK/BLK, BNIP3, BNIP3L/NIX, NOXA, PUMA, and BID), and the effector proteins BAX, BAK, and BOK [25, 26].

Under normal conditions, the antiapoptotic proteins of the Bcl-2 family maintain BAX and BAK in their inactive state. In response to accumulating cellular stress, BH3-only proteins either neutralize these antiapoptotic proteins or directly activate BAX and BAK, ultimately triggering irreversible disruption of the mitochondrial membrane [27, 28]. Numerous signaling pathways associated with growth factors, oncogenes, DNA damage, and cellular stress converge on altering the balance between the pro- and antiapoptotic members of the Bcl-2 family. The second major level of apoptotic regulation is mediated by the tumor suppressor p53 widely known as the “guardian of the genome”, which is encoded by the *TP53* gene and frequently mutated in human cancers. Following DNA damage, p53 induces the expression of several proapoptotic factors, including PUMA, NOXA, and BAX, and can also translocate to mitochondria, where it directly interacts with Bcl-2 family proteins to promote activation of the mitochondrial apoptotic

pathway [27, 29, 30]. The proapoptotic protein ARTS contributes to p53 trafficking to mitochondria and facilitates its interaction with Bcl-XL [31]. Disruption of the ARF–MDM2–p53 regulatory axis, loss or dysfunction of p53, depletion of proapoptotic factors, and amplification or overexpression of Bcl-XL or MCL-1 can enable tumor cells to evade apoptosis and thereby contribute to resistance to anticancer therapy [26, 32].

When proapoptotic signals prevail, the cytosolic protein BAX and the mitochondria-associated protein BAK insert into the mitochondrial outer membrane and, upon oligomerization, form pores of variable size. This process, known as mitochondrial outer membrane permeabilization (MOMP), is rapid (typically occurring within 5-10 min), irreversible and affects all or nearly all mitochondria in a cell [33]. As a result, cytochrome *c* and other mitochondrial proteins are released into the cytosol, where cytochrome *c* participates in the assembly of the apoptosome together with APAF1 (apoptotic peptidase activating factor 1) and caspase-9 (CASP9), leading to the activation of the effector caspases-3 (CASP3) and caspase-7 (CASP7). Under normal conditions, the antiapoptotic protein XIAP (X-linked inhibitor of apoptosis protein) is also present in the cytosol. XIAP binds to CASP9 and the effector caspases CASP3 and CASP7 and can thereby suppress apoptosis even after cytochrome *c* has been released from the mitochondrial intermembrane space. This inhibition of the caspase cascade is relieved by SMAC/DIABLO, which is released from damaged mitochondria together with cytochrome *c*, as well as by other negative regulators of IAP (inhibitors of apoptosis proteins) family proteins, including OMI and ARTS [31, 33]. Under some circumstances, cells undergo limited MOMP, when MOMP occurs in only a small subset of mitochondria. This may be insufficient to trigger cell death but can nevertheless increase the activity of mitochondrial nucleases, thereby promoting chromosomal instability. Cells that survive limited MOMP have also been reported to exhibit multidrug resistance [34].

If apoptosome formation is impeded and the caspase cascade is blocked, global MOMP can nevertheless trigger caspase-independent, apoptosis-like cell death, e.g., oxeiptosis and parthanatos. A key mediator of these processes is apoptosis-inducing factor (AIF, encoded by the *AIFM1* gene), which translocates from mitochondria to the nucleus, where it induces chromatin condensation and fragmentation [33]. Oxeiptosis is initiated under conditions of severe oxidative stress and involves the KEAP1–NRF2–PGAM5–AIF axis. Under moderate oxidative stress, NRF2 (nuclear factor erythroid 2-related factor 2) activation promotes antioxidant defense, while damaged mitochondria can be eliminated through mitophagy, thereby facilitating cellular adaptation and survival. However, when oxidative damage becomes excessive, AIF can be mobilized from mitochondria and contributes to the execution of apoptosis-like cell death [19].

Parthanatos critically depends on the hyperactivation of PARP1, which typically occurs in response to extensive DNA damage. Excessive accumulation of poly(ADP-ribose) (PAR) leads to energy depletion, suppresses glycolysis, impairs mitochondrial function, and promotes AIF translocation from mitochondria to the nucleus, ultimately leading to fragmentation of the nuclear genome. Unlike classical apoptosis, parthanatos is characterized by profound metabolic failure, cell swelling, and, ultimately, loss of plasma membrane integrity, thereby exhibiting features that overlap with both apoptotic and necrotic forms of cell death [35]. Parthanatos is of particular interest in oncology because PARP1 hyperactivation can promote tumor cell death, whereas pharmacological PARP inhibition can increase genomic instability and induce selective cytotoxicity in tumors with defects in DNA repair pathways [36].

The extrinsic pathway of apoptosis, immune-mediated apoptosis, and apoptosis associated with mitotic catastrophe. A distinctive feature of the extrinsic apoptotic pathway is its dependence on the activation of membrane-bound death receptors of the TNFR superfamily, including TNFRSF1A (TNFR1), FAS (CD95), and DR3/4/5 (Fig. 1; Table S1 in Online Resource 1). The binding of the corresponding death ligands (TNFα, FAS-L, and TRAIL, respectively) promotes the formation of oligomeric death-inducing signaling complexes (DISCs), which recruit adaptor proteins such as FADD, TRADD, and TRAF2, as well as initiator caspases, most prominently caspase-8 (CASP8). Subsequent activation of the effector caspases CASP3 and CASP7 produces the characteristic morphological and biochemical changes associated with apoptosis [37]. In addition to the canonical death receptors, apoptosis induced by growth factor deprivation can involve signaling through receptors such as c-MET, ALK, TrkA/TrkC (NTRK1/3), RET, EphA4, EphB3, IGF1R, c-KIT, PTCH1, CDON, and NOTCH, among others [38]. Signaling through the TNFR1 pathway is particularly important because, depending on the cellular and immune context and the status of intracellular regulatory mechanisms, it can direct cells toward different RCD outcomes. Thus, activation of the TNF signaling through the TRADD/RIPK1/TRAF2/cIAP complex can promote NF-κB-dependent cell survival and inflammatory responses. Conversely, changes in the composition or regulation of these signaling complexes can shift the response toward apoptosis or necroptosis [37, 39].

The extrinsic and intrinsic apoptotic pathways are closely interconnected. CASP8 can cleave and activate the BH3-only protein BID, thereby promoting

MOMP and engaging the intrinsic, mitochondrial apoptotic pathway. While this mitochondrial pathway involvement is dispensable in some cell types, it is essential in others, where full execution of extrinsic apoptosis critically depends on mitochondrial involvement and subsequent release of proapoptotic factors [40].

A distinct form of apoptosis is associated with signaling from the complex comprising caspase-2 (CASP2), its adaptor protein RAIDD, and the centromeric protein PIDD, collectively known as the PIDDosome. PIDDosome assembly is typically triggered by chromosome nondisjunction during mitosis. Under these conditions, CDK1-mediated inhibition of CASP2 is relieved, while the activated PIDDosome promotes p53 stabilization and directs the damaged cell toward apoptosis, which subsequently proceeds through the intrinsic pathway [33, 41]. This form of RCD is considered an important barrier to the survival of cells harboring severe mitotic defects and chromosomal instability.

Final stages of apoptosis: consequences of caspase activation, efferocytosis, and cell death associated with uptake by another cell. The activation of the effector caspases CASP3 and CASP7 represents a critical execution step common to both the extrinsic and intrinsic apoptotic pathways (Fig. 1). These caspases cleave a broad range of cellular substrates, leading to DNA fragmentation, cytoskeletal rearrangement, formation of apoptotic bodies, and exposure of cell surface signals that facilitate recognition and clearance by phagocytes [24, 33]. Among these signals, the most important is the lipid marker phosphatidylserine (PS), which is translocated from the inner to the outer leaflet of the plasma membrane. Together with other molecular signals, surface-exposed PS promotes the recruitment of macrophages and other phagocytic cells. The subsequent engulfment and clearance of apoptotic bodies, a process known as efferocytosis, prevents the release of intracellular components and proinflammatory mediators into the extracellular space and thereby generally limits inflammation. However, the immunological consequences of apoptosis are strongly context-dependent. Classical efferocytosis is associated with the establishment of an anti-inflammatory and tolerogenic microenvironment. Cells undergoing apoptosis, as well as macrophages and dendritic cells that engulf them, can contribute to the production and release of immunoregulatory mediators, including transforming growth factor-β (TGF-β). When the timely clearance of apoptotic cells is impaired, CASP3-mediated cleavage of gasdermin E (GSDME), the key effector enzyme of pyroptosis, promotes plasma membrane rupture in dying cells (see below). The resulting "secondary necrosis" is accompanied by the extracellular release of DAMPs and can elicit a pronounced inflammatory response [37, 42].

It should be emphasized that the presence of a whole cell or its fragments within another cell is not restricted to the terminal stages of apoptosis. In some cases, a phagocyte engulfs a viable cancer cell in a process known as phagoptosis. The internalized cell may subsequently die as a result of lysosomal degradation or activate its own cell death programs, including autophagy or apoptosis [43]. In other instances, the so-called cell-in-cell (CIC) structures are formed in which the internalized cell remains viable for a variable period of time. During emperipolesis, for example, the "victim" cell may persist within a host cell, sometimes of a different histological type, without undergoing immediate death and may subsequently exit the host cell. In contrast, during entosis, the internalized cell becomes enclosed within an entotic vacuole that subsequently fuses with lysosomes, resulting in the cell degradation [44]. The fate of the internalized cell depends on the metabolic state of the host cell, in particular, on amino acid availability and mTOR activity. Recent studies have also associated CIC structures with enhanced glycolysis and reduced cytotoxic T-cell responses [45]. In entosis, the survival of the internalized cell has been linked to gain-of-function mutations in *TP53* [46]. Another related phenomenon is cell cannibalism, in which a tumor cell actively surrounds and engulfs another cell, such as a lymphocyte or another component of the tumor microenvironment. Following formation of an intracellular vacuole, the engulfed cell is degraded by lysosomal enzymes [47]. It has been proposed that the degradation of engulfed cell may provide nutrients to the cancer cell, thereby supporting its survival under conditions of nutrient deprivation. In addition, the formation of CIC structures has been associated with epithelial–mesenchymal transition and acquisition of the dormant phenotype [48]. In tumors, these processes may contribute to therapeutic resistance and immune evasion; however, their prevalence and clinical significance remain poorly understood [47, 48].

Therapeutic potential. Since apoptosis is the most common form of RCD, it is not surprising that virtually all antitumor therapies engage apoptosis, either directly or indirectly, as a major mechanism of tumor cell elimination. Moreover, some drugs are specifically designed to target individual components of the apoptotic machinery.

The most successful therapeutic developments have focused on the inhibition of Bcl-2. The Bcl-2-selective BH3 mimetic venetoclax (ABT-199) has demonstrated substantial efficacy, particularly in hematologic malignancies [49]. In the phase III CLL14 clinical trial, a combination of venetoclax with the CD20 inhibitor obinutuzumab resulted in a markedly higher

five-year progression-free survival (PFS) rate than the standard chlorambucil–obinutuzumab regimen (63% vs. 27%, respectively) [50]. In acute myeloid leukemia, a combination of venetoclax and azacitidine likewise improved overall survival compared with azacitidine monotherapy [51]. In relapsed/refractory multiple myeloma, incorporation of venetoclax into the treatment regimens nearly doubled the PFS, although this benefit was accompanied by severe side effects [52]. By contrast, venetoclax-containing regimens have shown no efficacy in several solid tumors (NCT03900884, NCT04543916, VERONICA). One proposed explanation for the limited activity of venetoclax in these tumors, including solid neoplasms, is the compensatory role of other antiapoptotic proteins, particularly Bcl-XL and MCL-1. Acquired resistance may likewise be associated with upregulation of MCL-1, resulting in a shift in the tumor cell dependence from Bcl-2 toward alternative antiapoptotic pathways [53]. Consequently, efforts have focused on developing and introducing next-generation, potentially better-tolerated selective Bcl-2 inhibitors, such as sonrotoclax and lisaftoclax, as well as inhibitors targeting Bcl-XL and MCL-1 [54]. However, systemic inhibition of Bcl-XL is limited by thrombocytopenia, reflecting the essential role of Bcl-XL in platelet survival. To mitigate this toxicity, strategies based on selective Bcl-XL degradation using PROTAC technology have been proposed [26].

Thus, Bcl-2 overexpression alone does not necessarily confer sensitivity to venetoclax, as therapeutic efficacy is determined by a broader configuration of the apoptotic network. This underscores the potential value of integrative approaches for assessing the overall "apoptotic readiness" of tumors, which may provide more informative predictive insights than the analysis of individual molecular or genetic biomarkers [55]. Accordingly, combining Bcl-2 inhibitors with chemotherapy, targeted agents, or other antitumor interventions may offer greater therapeutic potential than their use as monotherapy [56, 57].

Another approach to the pharmacological modulation of apoptosis involves SMAC (second mitochondrial activator of caspase) mimetics, which relieve the inhibition of caspases mediated by IAPs, including xevinapant (Debio-1143), birinapant (TL32711), and tolinapant (ASTX660) [58, 59]. Their therapeutic potential extends beyond direct enhancement of apoptotic signaling, as these agents can also modulate TNF-dependent signaling pathways and influence interactions between tumor cells and the immune system. However, results of clinical trials have thus far been inconsistent. In particular, the failure of the phase III TrilynX trial of xevinapant illustrates that targeting individual components of the apoptotic network does not necessarily translate into clinical benefit and may produce context-dependent effects influenced by the composition of the tumor microenvironment [60]. Similarly, pharmacological activation of the extrinsic apoptotic pathway has yet to achieve the anticipated clinical efficacy. Agonists targeting TRAIL receptors, such as dulanermin and mapatumumab, have demonstrated limited clinical efficacy, potentially due to heterogeneous receptor expression, defects in apoptotic signaling and caspase activation in tumor cells, and compensatory engagement of antiapoptotic pathways [61].

A separate line of research focuses on pharmacological strategies to engage or restore p53 function. Thus, MDM2/MDMX inhibitors are being developed to stabilize p53 and increase the likelihood of apoptosis in tumors retaining wild-type *TP53*. Although clinical trial results have so far been discouraging, the biological rationale for this approach remains compelling [62]. A complementary strategy involves restoring the function of mutant p53 through pharmacological reactivation [63].

NECROPTOSIS AND PANoptosis: A SYNTHESIS OF CELL DEATH CASCADES

Already during the early studies of the extrinsic apoptotic pathway, it became evident that activation of death receptors by cognate ligands, such as TNFα, can induce not only apoptosis but also a form of RCD that is morphologically indistinguishable from necrosis [64]. Subsequent research has characterized this caspase-independent form of RCD, now termed necroptosis, which is associated with cell swelling, organelle dysfunction, plasma membrane rupture, and the release of inflammatory mediators (Table S1 in Online Resource 1). Execution of the necroptotic program requires the formation of a TRADD–TRAF–RIPK1/FADD–RIPK1 signaling complex following the binding of the death ligand to its cognate death receptor. This pathway is favored when the expression of CASP8 is reduced (otherwise, apoptosis is preferentially initiated). In addition, RIPK1 must avoid polyubiquitination by cellular IAPs (cIAP1/2), as this modification promotes NF-κB activation rather than necroptotic signaling. FLIP represents another important negative regulator of necroptosis. CASP8/FLIP heterodimers lack the ability to proteolytically activate new procaspase-8 molecules but can cleave RIPK1 and RIPK3.

The role of RIPK1 in the execution of necroptosis involves its interaction with and activation of another kinase, RIPK3, a key initiator of the necroptotic pathway. Oligomerization of RIPK1 and RIPK3 leads to the necrosome formation (Fig. 1). RIPK3, in turn, phosphorylates MLKL, a pseudokinase that subsequently oligomerizes and forms membrane-disrupting

structures. These structures compromise the integrity of the plasma membrane from within and may also promote the translocation of PS to the outer leaflet of the membrane. Membrane rupture results in the release of numerous DAMPs, thereby stimulating the production of proinflammatory and/or immune-modulating cytokines. Ultimately, the cellular debris must be cleared by phagocytic cells, including macrophages and dendritic cells [11, 65]. According to recent findings, however, the terminal rupture of the plasma membrane during necroptosis may not be mediated directly by MLKL. Instead, it has been proposed that this process involves the SIGLEC12 protein: a dephosphorylated fragment of SIGLEC12 binds to MLKL and forms a fibrillar structure capable of disrupting the plasma membrane. In tumor cells, SIGLEC12 may be inactivated by somatic mutations, potentially preventing the execution of necroptotic cell death [66]. Numerous approaches have been investigated at the preclinical stage to induce necroptosis therapeutically, including nanoparticles carrying necroptosis-inducing agents and nanomaterials designed to deliver MLKL mRNA. However, translating these strategies into clinical practice in the medium term appears unlikely [67].

Another route of RIPK3 activation involves its direct interaction with ZBP1/DAI, an intracellular sensor of nucleic acids capable of adopting a Z-conformation, such as viral DNA and DNA fragments released by cancer cells. Finally, activation of interferon receptors can also induce necroptosis through a mechanism that remains poorly understood [11, 68]. Notably, when CASP8 is available and oncogenic pro-survival signals are absent, RIPK3 can recruit RIPK1 to form a ZBP1–RIPK3–RIPK1–CASP8–FADD complex that is functionally analogous to DISC, thereby promoting apoptosis through the extrinsic pathway. The adaptor protein ASC may also be recruited to this complex, facilitating inflammasome assembly and triggering RCD via the pyroptotic pathway [11].

Relatively recently, a “synergistic” form of RCD was described that involves large protein complexes incorporating various adaptor proteins and markers of apoptosis, necroptosis, and pyroptosis, including caspases, RIPK1, RIPK3, ASC, and NLRP3/NLRP12. This form of cell death was termed PANoptosis (PAN: pyroptosis, apoptosis, and necroptosis) [69] (Fig. 1). PANoptosome activation can result in cell survival or cell death through one or a combination of these three pathways and is generally accompanied by a burst of proinflammatory cytokine production. PANoptosomes vary in their molecular composition, and their assembly in response to pathogenic microorganisms, DAMPs, PAMPs, or Z-DNA/RNA is initiated by sensor proteins such as ZBP1, AIM2, NLRP12/NLRC5, and NLRP3. In some contexts, the interaction of RIPK1 and RIPK3, with subsequent recruitment of NLRP3, ASC, caspase-1 (CASP1), and CASP8, appears to be sufficient to initiate PANoptosome formation [70]. The main positive regulator of PANoptosis is the interferon-inducible transcription factor IRF1, which, among its other functions, promotes the expression of ZBP1, AIM2, NLRP12, and RIPK1 [71]. The biological significance of the distinct PANoptosome variants, however, remains unclear. One possibility is that these variants represent different states within a dynamic equilibrium, with their composition and activity shifting according to the initial abundance of individual components and their respective rates of recruitment and consumption.

Given the high immunogenicity of dying cells, induction of PANoptosis has emerged as a potentially promising therapeutic strategy [72, 73]. However, to date, these experimental approaches have not progressed to clinical trials.

AUTOPHAGY: FROM A CELL SURVIVAL MECHANISM TO A THERAPEUTIC TARGET IN ONCOLOGY

Since the discovery of autophagy by Christian de Duve [74], our understanding of its mechanisms and biological functions has changed considerably. Today, autophagy is regarded not simply as a specialized form of starvation-associated cell death, but as a central regulator of cellular responses to stress that influences the balance between survival and various forms of RCD [75]. Morphologically, autophagy involves the sequestration of cytoplasmic components within double-membrane structures, termed autophagosomes, which subsequently fuse with lysosomes, enabling the degradation and recycling of macromolecules (Table S1 in Online Resource 1). Under physiological conditions and in response to stresses such as nutrient deprivation, hypoxia, or oxidative stress, this process facilitates organelle turnover and the removal of damaged or potentially toxic protein aggregates and cellular structures [76]. However, under conditions of severe or irreparable cellular damage, excessive autophagic activity may contribute to extensive cellular self-digestion and cell death, with the release of nutrients and DAMPs into the microenvironment. These processes can promote the redistribution of resources and influence the maintenance of tissue and cell population homeostasis [77, 78].

Autophagy is generally classified into three major types according to the mechanisms by which intracellular material is sequestered: macroautophagy, microautophagy, and chaperone-mediated autophagy [79]. Macroautophagy is the most common form that involves the formation of a double-membrane

isolation structure, the phagophore, which then fuses with a lysosome, where its contents are degraded by an array of hydrolytic enzymes, including cathepsins, acid hydrolases, lipases, and nucleases. This mechanism is engaged when a cell needs to be destroyed. Through selective autophagy, damaged, dysfunctional, or superfluous organelles can be targeted for degradation, including mitochondria (mitophagy), ribosomes (ribophagy), and the endoplasmic reticulum (reticulophagy). Likewise, protein and lipid aggregates can be selectively removed through processes such as ferritinophagy and lipophagy, while intracellular pathogens can be eliminated through xenophagy [80]. Dysregulation of selective autophagy has been implicated in carcinogenesis and pathogenesis of neurodegenerative disorders and metabolic diseases. These findings have stimulated efforts to identify and develop low-molecular-weight autophagy modulators capable of promoting selective degradation of specific intracellular substrates [81].

Both normal and malignant cells generally benefit from autophagy because of its essential role in maintaining cellular homeostasis under adverse environmental conditions. However, this protective function can exert opposing effects at the level of the whole organism in normal cells, autophagy can prevent malignant transformation, whereas after malignant transformation, it may support tumor progression and resistance to therapy [82, 83]. Indeed, instances have been described in which elevated autophagic activity suppressed other forms of RCD, thereby facilitating malignant transformation and accelerating tumor progression [84, 85]. For example, autophagy has been shown to selectively degrade major histocompatibility complex class I (MHC-I) molecules in pancreatic cancer cells, thereby impairing their recognition by the immune system [86]. Autophagic processes also substantially influence the inflammatory and immune microenvironment, with effects that can either promote or restrain tumor growth, depending on the cellular and pathological context [87, 88].

Molecular mechanisms and regulatory systems. Macroautophagy is a multistep cellular process involving the formation and maturation of a specialized organelle – the autophagosome. Its molecular organization can be broadly divided into four functional levels: (1) cellular stress sensors, (2) autophagy-initiating complexes, (3) the molecular machinery responsible for autophagosome formation, elongation, and maturation, and (4) systems mediating the transport and degradation of autophagosomal cargo [89]. The core macroautophagy machinery comprises 15-18 conserved autophagy-related (ATG) proteins. Rather than functioning as independent molecules, these proteins are organized into six highly coordinated and interconnected functional modules: the ULK1 complex, the class III phosphatidylinositol 3-kinase complex I (PI3KC3-C1), the LC3/ATG8 conjugation system, the PI3P-binding proteins of the WIPI family, the ATG2 lipid-transfer complex, and the membrane scramblase ATG9 (Fig. 1) [90, 91]. This modular organization provides a framework for the pharmacological regulation of autophagy in cancer.

mTORC1 is a central negative regulator of autophagy, which integrates signals from insulin and IGF-1, the PI3K (phosphatidylinositol 3-kinase)–AKT pathway, amino acid sensors (SESN2, CASTOR1, and SLC38A9), and growth factors. Under sufficient nutrient supply, active mTORC1 phosphorylates ULK1 and ATG13, thereby suppressing autophagy initiation. Conversely, during nutrient starvation or energy stress, AMPK is activated, leading to simultaneous inhibition of mTORC1 and activation of the ULK1 complex through phosphorylation of its components. The ULK1 complex is recruited to specialized regions of the endoplasmic reticulum, where it promotes formation of the isolation membrane, or phagophore, by phosphorylating components of the nucleation complex, including class III phosphatidylinositol 3-kinase (PI3KC3), VPS34, Beclin-1 (BECN1), VPS15, ATG14L, and AMBRA1 [92]. This complex catalyzes the local production of phosphatidylinositol 3-phosphate (PI3P), which functions as a membrane platform for the recruitment of WIPI family proteins, DFCP1, and other PI3P-binding effectors [93]. Subsequent phagophore expansion and closure are mediated by coordinated actions of ATG2, the ATG12–ATG5–ATG16L1 complex, and the LC3A/B/C–ATG4/7/3 and GABARAP conjugation systems. Finally, phagophore fusion with the lysosome is facilitated by STX17, SNAP47, and VAMP7/8 [94, 95].

Because of extensive molecular crosstalk, autophagy signaling is closely interconnected with virtually all major forms of RCD, including apoptosis, necroptosis, pyroptosis, and ferroptosis, as well as less common forms such as entosis (the engulfment of one cell by another), parthanatos, and oxeiptosis [96-99]. This complex regulatory network is coordinated by several master regulators, including p53, HIF-1α, MYC, mTOR, AMPK, Bcl-2, p62/SQSTM1, and AMBRA1 [100-102]. This extensive interdependence helps explain why pharmacological modulation of autophagy in oncology can produce context-dependent and sometimes opposing effects.

A key regulatory node of the apoptosis–autophagy switch is the Bcl-2/Beclin-1 complex. Under basal conditions, the antiapoptotic protein Bcl-2 binds Beclin-1, thereby inhibiting the autophagy machinery. In response to cellular stress, this complex is disrupted, in part through the action of the kinase JNK1. The resulting release of Beclin-1 promotes phagophore formation by activating PI3KC3/Vps34, whereas free Bcl-2 continues to interact with the proapoptotic

proteins BAX and BAK, thereby restraining apoptosis. When cellular stress reaches a critical level, initiator and effector caspases become activated and cleave key autophagy-related proteins, including Beclin-1 and ATG5, turning them into proapoptotic factors, thus shifting the balance toward apoptosis and ultimately leading to cell death [103, 104].

The switch from autophagy to ferroptosis depends on ferritinophagy, which is a selective autophagic degradation of ferritin mediated by the cargo receptor NCOA4. This process increases the pool of labile Fe^{2+}, promotes the accumulation of reactive oxygen species (ROS), and drives extensive lipid peroxidation, ultimately triggering ferroptosis (see section "Ferroptosis: The Response to Oxidative Stress") [105]. The transition between the autophagy/necroptosis scenarios is regulated by the RIPK1/RIPK3/MLKL signaling axis, which can initially promote protective mitophagy but, when excessively activated, shifts the cellular response toward destructive self-digestion and cell lysis [106]. In cancer cells, the balance between these pathways determines whether tumor cells adapt to metabolic stress and survive or instead undergo necroptosis or immunogenic cell death [107].

Therapeutic potential. The therapeutic potential of autophagy depends on whether its inhibition or induction is more appropriate, which in turn is determined by the biological characteristics and stage of the tumor [75, 108]. Many tumors exploit autophagy, particularly mitophagy, as an adaptive mechanism that promotes resistance to chemotherapy, radiotherapy, and targeted therapies [109]. For example, Beclin-1 overexpression has been implicated in resistance to cetuximab in colorectal cancer [110], EGFR inhibitors in lung cancer [111], and doxorubicin in osteosarcoma [112]. In such cases, inhibition of Beclin-1 and other components of the autophagic machinery using pharmacological agents (e.g., bafilomycin A1 and 3-methyladenine) or regulatory RNAs (miR-1, miR-30, miR-34a, miR-101, lncRNA HOTAIR, and BLACAT1) may restore the sensitivity of tumor cells to anticancer treatments [75, 113-116]. Mechanistically, pharmacological blockade of autophagy promotes the accumulation of damaged mitochondria, ROS, and toxic protein aggregates, thereby enhancing apoptosis, ferroptosis, and other forms of RCD. Chloroquine and hydroxychloroquine (Plaquenil) are among the most extensively studied pharmacological inhibitors of autophagy; they have shown promising results in phase I-III clinical trials when combined with chemotherapy, radiotherapy, or targeted therapies [117, 118]. However, neither drug has been approved by the FDA for the treatment of malignant neoplasms, largely because of their limited specificity and the risk of treatment-related adverse effects, including hepatotoxicity, cardiotoxicity, neutropenia, thrombocytopenia, myopathy, and retinopathy [119, 120]. Consequently, current efforts in anticancer drug development are increasingly focused on more selective autophagy-targeting strategies, including inhibitors of ULK1, VPS34, and ATG7 (e.g., PF-03814735 and 3-methyladenine [3-MA]), lysosomal inhibitors (bafilomycin A1), and low-molecular-weight compounds that selectively modulate autophagy subtypes with prosurvival functions [81, 109, 121, 122].

The induction of autophagy may also have therapeutic implications in cancer. At early stages of tumor development, autophagy activation can promote the elimination of transformed cells or increase their sensitivity to cytotoxic agents. In addition, autophagy can reduce the abundance of proteins that support tumor growth and enhance antitumor immune responses within the tumor microenvironment [109]. For example, rapamycin (sirolimus), an mTOR inhibitor that releases the inhibitory "brake" on the autophagic pathway, has already been introduced into clinical practice [123]. Other targeted agents include temsirolimus, everolimus, ridaforolimus, torin-1, and GDC-0980 [124]. Temsirolimus has been approved by the FDA for the treatment of advanced renal cell carcinoma [125]. Ridaforolimus (AP23573, deforolimus) has been evaluated in a phase III clinical trial for the treatment of sarcomas (NCT00538239). GDC-0980 has been investigated in phase II clinical trials involving patients with renal cancer (NCT01442090) and non-Hodgkin lymphoma (NCT00854126, NCT00854152), as well as endometrial (NCT01455493) and breast cancers (NCT01254526). In preclinical studies, metformin, an FDA-approved antidiabetic agent, has also demonstrated the ability to activate autophagy through AMPK signaling. In combination with temsirolimus, metformin produced a moderate synergistic antitumor effect in a phase I clinical trial involving patients with advanced or recurrent endometrial cancer (NCT01529593). Interestingly, curcumin, a well-known chemopreventive compound, has been shown to induce autophagy and promote glioblastoma cell death, as demonstrated by an increased number of LC3-positive autophagosomes and elevated expression of ATG5 and ATG7 [126].

The ambiguity surrounding the therapeutic potential of autophagy modulation, together with the complexity of context-dependent mechanisms governing the survival of distinct tumor cell populations, is illustrated by the results of the CLEVER clinical trial in breast cancer survivors with detectable disseminated tumor cells in bone marrow aspirates [127]. In this trial, two agents with seemingly opposing effects on autophagy were administered concomitantly: the mTOR inhibitor everolimus, which stimulates autophagy, and the lysosomal inhibitor hydroxychloroquine, which blocks autophagic flux at its terminal stage.

The rationale underlying this combination is that consistently increasing the dependence of tumor cells on autophagy and subsequently preventing autophagy completion may promote the elimination of disseminated tumor cells and prevent their escape from dormancy. In accordance with this hypothesis, the CLEVER trial reported a significant reduction in the number of dormant tumor cells detected in bone marrow aspirates, accompanied by a 100% three-year relapse-free survival rate.

Considerable interest has emerged in the combined use of autophagy modulators and immunotherapy. Pharmacological modulation of autophagy has been shown to reshape the composition and functional state of the tumor microenvironment, enhance tumor antigen presentation, promote the infiltration of cytotoxic $CD8^+$ T lymphocytes into tumors, attenuate the immunosuppressive activity of tumor-associated macrophages and myeloid-derived suppressor cells, and potentially overcome resistance to immune checkpoint inhibitors [128].

PYROPTOSIS: IMMUNOGENIC CELL DEATH

Pyroptosis is an inflammatory form of RCD characterized by cell swelling, the formation of gasdermin pores in the plasma membrane, subsequent membrane rupture, and the release of numerous proinflammatory mediators, including IL-1β and IL-18, as well as DAMPs, such as the non-histone nuclear protein HMGB1, ATP, and free nuclear and mitochondrial DNA [129]. In contrast to apoptosis, which is generally considered immunologically silent, the products of pyroptosis actively promote the recruitment and activation of both innate and adaptive immune cells [130]. Thus, pyroptosis serves not only as a mechanism for eliminating infected or transformed cells but also as an important link between cell death and immune response. Increasing evidence indicates that pyroptosis plays a pivotal role in antitumor immunity and that its targeted induction may represent a promising therapeutic strategy. Beyond directly promoting tumor-cell death, pyroptosis can enhance tumor immunogenicity and potentially improve the efficacy of anticancer treatments, particularly immunotherapeutic approaches [131].

Molecular mechanisms and regulatory systems. Originally, pyroptosis was defined as a CASP1-dependent inflammatory form of RCD [132]. However, in 2015, gasdermin D (GSDMD) was identified as the key executioner of pyroptosis [133]. In humans, the gasdermin family comprises six proteins: GSDMA, GSDMB, GSDMC, GSDMD, GSDME, and DFNB59 (PJVK). With the exception of DFNB59, these proteins share a conserved two-domain architecture consisting of the N-terminal pore-forming domain and the C-terminal autoinhibitory domain. Gasdermins are activated through proteolytic cleavage of the interdomain linker by specific proteases [134]. Following cleavage, the liberated N-terminal domain translocates to the plasma membrane, where it oligomerizes and forms large transmembrane pores. The formation of these pores disrupts cellular osmotic homeostasis, leading to cell swelling, eventual membrane rupture, and release through the pores of pro-inflammatory mediators, particularly interleukins IL-1β and IL-18, hereby promoting inflammation and influencing the surrounding microenvironment [135].

The canonical pyroptosis pathway is initiated by the activation of inflammasomes in response to the recognition of PAMPs or DAMPs by specific sensor receptors [136] (Fig. 1, Table S1 in Online Resource 1). The stimuli that trigger inflammasome activation are diverse and reflect various forms of cellular danger signals, including: (i) decreased intracellular potassium or ATP levels, cholesterol crystals, uric acid, and ROS, which are indicative of cellular stress; (ii) the presence of double-stranded DNA in the cytosol, including viral or bacterial DNA and damaged self-DNA, indicating either genomic damage or intracellular invasion; and (iii) bacterial flagellin, modification or inactivation of Rho GTPases by bacterial toxins, foreign proteases, and intracellular lipopolysaccharide (LPS) from Gram-negative bacteria, which can signal pathogen invasion. Following recognition of these danger signals, specific inflammasomes are activated, each characterized by a distinct sensor (NLRP1, NLRP3, NLRC4, AIM2, ZBP1, pyrin, or CARD8). The non-canonical inflammasome pathway involving CASP4/5/11 can be activated directly by cytosolic LPS, without requiring an upstream pattern-recognition receptor [137]. Inflammasome activation subsequently promotes the activation and processing of CASP1 or the inflammatory caspases CASP4/5/11. These proteases cleave GSDMD and GSDME, thereby initiating the formation of membrane pores [138, 139]. Concurrently, CASP1 promotes the maturation of the proinflammatory cytokines IL-1β and IL-18 [140].

In neoplastic cells, pyroptosis can also be initiated through alternative, bypass pathways. For example, under conditions of GSDME overexpression, apoptotic stimuli can redirect the cell death program toward pyroptosis. In this case, the apoptotic effector caspases CASP3 and CASP7 directly cleave GSDME, resulting in plasma membrane rupture and the subsequent release of DAMPs and inflammatory cytokines [141].

An important role in antitumor immunity is played by the activation of gasdermins by $CD8^+$ T lymphocytes and natural killer (NK) cells through the secretion of granzymes. Granzyme A can directly

activate GSDMB, whereas granzyme B promotes GSDME cleavage either directly or indirectly through the activation of CASP3. Thus, pyroptosis represents an additional mechanism of lymphocyte-mediated cytotoxicity that complements the classical pathways involving perforin and the Fas/FasL system [142, 143]. In the tumor microenvironment, pyroptosis can exert a pronounced immunostimulatory effect. The destruction of tumor cells is accompanied by the release of tumor antigens, DAMPs, and various chemokines, which promote maturation of dendritic cells and enhance the presentation of tumor-associated neoantigens [65, 143]. In parallel, inflammasome activation in dendritic cells and macrophages induces the production of IL-1β and IL-18, thereby promoting the recruitment of cytotoxic lymphocytes and supporting the development of a Th1-type immune response [145, 146]. Consequently, pyroptosis has a potential to convert immunologically "cold" tumors, characterized by limited immune cell infiltration, into "hot" tumors with enhanced lymphocytic infiltration and, potentially, greater sensitivity to immune checkpoint inhibitor therapy [147, 148]. However, the same inflammatory processes that can enhance antitumor immunity may also produce adverse effects. When pyroptosis is prolonged or occurs at low intensity, chronic release of IL-1β, IL-18, and other inflammatory mediators may promote angiogenesis, remodeling of the tumor microenvironment, and the establishment of an immunosuppressive niche [140, 149]. Among these mediators, IL-1β, a major downstream product of NLRP3 inflammasome activation, appears to be particularly important. It can stimulate the expansion of cancer stem cells through activation of the Smad/ID1 axis and promote epithelial–mesenchymal transition and metastatic progression. In addition, IL-1β facilitates the recruitment of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) to the tumor microenvironment, thereby contributing to the suppression of antitumor immune responses [137, 150-152]. Thus, the biological consequences of pyroptosis depend not only on the occurrence of cell death itself but also on the magnitude, duration, and spatiotemporal context of the associated inflammatory response. Such a diversity of possible scenarios complicates efforts to exploit controlled pyroptosis induction as an anticancer strategy. Nevertheless, approaches aimed at harnessing pyroptosis for therapeutic purposes are actively being investigated.

Therapeutic potential. The therapeutic use of pyroptosis-modulating drugs in clinical oncology is a promising concept; however, its clinical translation remains at an early stage. As of August 2026, no registered interventional oncology trials in the ClinicalTrials.gov registry specifically indicate the therapeutic induction of pyroptosis or direct modulation of gasdermin-mediated cell death as a primary therapeutic objective. Available clinical evidence has been generated predominantly in studies of established anticancer modalities, including CAR-T cell therapy, PARP inhibitors, antiangiogenic agents, chemotherapy, and immune checkpoint inhibitors. In these studies, pyroptosis is generally regarded as one of the mechanisms contributing to the activation of the cytotoxic immune microenvironment and, consequently, to the antitumor effects of treatment, rather than as an independent therapeutic target [129, 137, 144].

Promising experimental and clinical evidence has emerged supporting the therapeutic induction of pyroptosis in anaplastic thyroid carcinoma. In particular, a combination of low-dose apatinib (VEGFR2 inhibitor) with melittin (pyroptosis inducer isolated from bee venom) was shown to simultaneously activate the canonical and non-canonical pyroptotic pathways mediated by CASP1/GSDMD and CASP3/GSDME. This dual activation resulted in a pronounced synergistic antitumor effect [153]. However, the major obstacle to incorporating pyroptosis inducers into therapeutic regimens is their substantial hemolytic toxicity. To enable the application of melittin and related agents in oncology, these compounds can be encapsulated in specialized polymeric nanoparticles, such as liposomes or polymersomes, or conjugated to tumor-targeting antibodies. These delivery strategies are designed to promote peptide activity selectively within the tumor while minimizing the damage to healthy tissues [154, 155]. Co-encapsulation of melittin with a conventional chemotherapeutic agent, such as doxorubicin, has also shown promise. Such co-delivery can produce highly elevated, tumor-selective concentrations of the cytotoxic agent in cancer cells and, in some cases, help overcome acquired resistance to therapy [156, 157].

It is important to note that artificial nanovesicles, including metal-containing, silicone-, graphene-, and hydrogel-based nanomaterials, can induce pyroptosis even in the absence of a therapeutic cargo and thereby serve as tools for initiating this program in neoplastic cells or reprogramming immune components of the tumor microenvironment [158]. Current research on nanomaterial-induced pyroptosis encompasses several approaches, including nanoparticle-mediated magnetic hyperthermia, photothermal therapy, targeted modulation of tumor metabolism, chemotherapeutic drug delivery, and multimodal strategies that combine multiple therapeutic mechanisms [159, 160].

It is believed that the evasion of pyroptosis by tumor cells represents one of the immune escape mechanisms. The most common mechanism of such evasion is the epigenetic suppression of gasdermin expression through promoter hypermethylation or the induction of alternative splicing, as reported for GSDMB [161].

DNA methyltransferase inhibitors, particularly decitabine (DAC), can restore GSDME expression and thereby increase the susceptibility of tumor cells to pyroptosis, which may contribute to the enhanced efficacy of chemotherapy [162]. To facilitate the targeted delivery of DAC to tumors, Yu et al. developed an innovative nanoparticle-based system employing neutrophil camouflage [163]. The nanocarrier consisted of bovine serum albumin conjugated to the photosensitizer IR820 and an antibody against the neutrophil marker CD11b, enabling targeted DAC delivery to the tumor while minimizing systemic toxicity. Upon reaching the tumor, the nanocarrier associated with neutrophils and, following photothermal activation of the photosensitizer, released its cargo locally. This treatment induced pyroptosis, stimulated the tumor immune microenvironment, and promoted an immunologically "hot" tumor phenotype. Consequently, the approach enhanced the efficacy of immunotherapy and reduced metastatic progression in mouse models of triple-negative breast cancer [163, 164]. DAC was the first (and so far, the only) pyroptosis-inducing agent to enter clinical trials. It has been evaluated in a phase 1/2 clinical trial in patients with the wild-type *KRAS* colorectal cancer in combination with the anti-EGFR monoclonal antibody panitumumab (NCT00879385) [165].

Another example of the clinical significance of pyroptosis is its role in CAR-T cell therapy. Liu et al. demonstrated that granzyme B released by CAR-T cells activated CASP3 and promoted GSDME cleavage in tumor cells, triggering pyroptosis. The resulting activation of macrophages through GSDMD subsequently induces the massive release of proinflammatory mediators and contributes to the development of cytokine release syndrome [166]. Thus, pyroptosis can both potentiate the antitumor efficacy of CAR-T therapy and contribute to its toxicity [167, 168]. These findings have prompted the development of precision strategies to limit GSDME activity, as well as approaches for the targeted delivery of pyroptosis inducers to small subpopulations of tumor cells and the modulation of macrophage activity to mitigate cytokine storms. However, to date, these approaches have been evaluated primarily in mouse models and cell lines [140].

Noticeable progress has also been made in enhancing the efficacy of PARP inhibitors (PARPi) through the induction of pyroptosis. Recent studies have demonstrated that PARPi-mediated tumor cell death occurs not only through the classical apoptotic pathway but also through activation of the GSDMC/GSDME–CASP8 pyroptotic cascade and recruitment of cytotoxic $CD8^+$ T lymphocytes [169-171]. Notably, high levels of GSDMC/GSDME expression have been identified as potential predictors of PARPi responsiveness across various cancer types and have been associated with the elimination of tumor cells irrespective of BRCA1 status or the functional state of the homologous recombination DNA repair (HRR) system [171, 172]. These findings have substantially broadened the understanding of the cytotoxic mechanisms of PARPi, extending their role beyond that of targeted cytostatic agents that exploit synthetic lethality in BRCA-deficient tumors to that of potential inducers of immunogenic cell death. Furthermore, this mechanism provides a basis for a novel therapeutic strategy aimed at prolonging treatment responses and overcoming PARPi resistance in tumors with restored or compensated HRR activity by promoting gasdermin expression [172].

The ability of pyroptosis to "set fire" to tumors by promoting the infiltration of immune effector cells may be exploited to enhance the efficacy of standard immunotherapies based on immune checkpoint inhibitors; however, approaches aimed at achieving this goal have thus far remained at the preclinical stage [173, 174]. A key prerequisite for translating these strategies into clinical trials is the identification of dosing regimens that induce robust immunogenic cell death while minimizing the risk of cytokine release syndrome and other hyperinflammatory complications. The substantial heterogeneity of gasdermin activity across tumor types and normal tissues further necessitates prospective molecular stratification of patients based on the expression levels of GSDMC, GSDMB, GSDMD, and GSDME, the activity of their regulators, and the epigenetic status of the corresponding genes. Equally important is the incorporation of serial liquid biopsy analyses into clinical trial protocols to dynamically monitor pyroptosis activation *in vivo*. Circulating fragments of gasdermin cleavage and pyroptosis-associated extracellular vesicles may serve as potential biomarkers for this purpose. Such an approach could not only provide evidence that the intended mechanism of drug action is engaged but also facilitate dose optimization for subsequent phases of clinical development. At the same time, careful monitoring of "off-tumor" pyroptosis will be essential, particularly in tissues characterized by high basal GSDME expression, where unintended activation of pyroptosis may increase the risk of systemic toxicity [11, 140].

FERROPTOSIS: THE RESPONSE TO OXIDATIVE STRESS

Ferroptosis is a specific metabolic program of cell death that joined the "big three" of RCD (apoptosis, necrosis, autophagy) relatively recently, in 2012. It was identified in the laboratory of Brent Stockwell

during investigations into the mechanisms of the cytotoxic activity of erastin in *RAS*-mutated fibrosarcoma cells [175]. Exposure to erastin induced an unusual form of death of tumor cells characterized by reduction in the mitochondrial volume, loss of cristae, and increased density of the outer mitochondrial membrane, followed by its rupture. In contrast to apoptosis, the nucleus remained largely intact, with no appreciable changes in nucleus size or chromatin condensation. At later stages, cells underwent swelling and membrane rupture, resembling necrotic cell death; in some cases, this process was accompanied by the formation of autophagosomes. Notably, this mode of cell death could be prevented and reversed by depletion of the labile intracellular Fe^{2+} pool, whereas classical apoptosis inhibitors, including the pan-caspase inhibitor Z-VAD-FMK, had no protective effect. This strict dependence on intracellular iron availability gave rise to the term “ferroptosis”. At the biochemical level, ferroptosis results from a disruption of the balance between the generation and detoxification of iron-dependent lipid peroxidation products. This imbalance leads to the progressive and ultimately irreversible accumulation of toxic phospholipid hydroperoxides, particularly polyunsaturated fatty acid (PUFA)-containing phospholipid hydroperoxides (PL-PUFA-OOH), culminating in catastrophic plasma membrane damage and cell rupture [176].

Ferroptosis plays an important role in maintaining cellular homeostasis and is involved in normal tissue morphogenesis and the regulation of embryonic stem cells. Increasing evidence indicates that ferroptosis-related biochemical pathways directly contribute to the development and function of the female reproductive system, regulating granulosa cell survival, oocyte maturation and preservation, and formation of the placenta [177]. Dysregulation of these pathways has been associated with several reproductive disorders, including polycystic ovary syndrome, premature ovarian insufficiency, endometriosis, preeclampsia, and spontaneous abortion [177]. Abnormalities in ferroptosis signaling have also been implicated in tumorigenesis. This association has been documented particularly in gynecological malignancies, including ovarian, cervical, endometrial, and breast cancers [178, 179]. At the same time, alterations in ferroptosis pathways have been reported in a wide range of other malignancies, including lung, renal, and gastric cancers, melanoma, and glioma [180-182]. Accordingly, ferroptosis is increasingly recognized as an important endogenous mechanism involved in tumor suppression.

Molecular mechanisms and regulatory systems. Unlike the RCD scenarios described above, the initiation of ferroptosis does not require specific trigger signals to initiate a defined biochemical cascade. Instead, this death program remains in a state of constitutive readiness and is normally restrained by metabolic systems that regulate the generation and detoxification of free radicals and lipid peroxides (Fig. 1, Table S1 in Online Resource 1). Under pathological or stress conditions, these protective mechanisms may fail, for example, through restriction of cystine import, depletion of glutathione (GSH), inhibition of glutathione peroxidase 4 (GPX4), disruption of the Xc^- (SLC7A11)–GSH–GPX4 axis, or inactivation of parallel antioxidant pathways. Consequently, ROS and lipid peroxides can accumulate to critical levels, leading to oxidative damage of membrane phospholipids and triggering uncontrolled lipid peroxidation [11, 176].

An excess of free divalent iron ions (Fe^{2+}) is required for ferroptosis initiation. Fe^{2+} catalyzes the Fenton reaction, generating highly reactive free radicals that attack membrane phospholipids [175, 183]. The intracellular labile iron pool is regulated through a series of coordinated biochemical steps. First, extracellular Fe^{3+} is taken up by endocytosis through transferrin (TF) and its cognate receptor (TFRC). Second, the metalloreductase STEAP3 reduces Fe^{3+} to Fe^{2+} in the endosome. Third, Fe^{2+} is transported from the endosome into the cytoplasm by DMT1 and subsequently into mitochondria via SFXN1, where it can react with H_2O_2 or endoperoxides such as FINO2 (ferroptosis-inducing agent with an endoperoxide moiety 2), catalyzing the formation of highly reactive hydroxyl and alkoxyl radicals. An alternative mechanism for increasing the cytosolic Fe^{2+} pool is ferritinophagy, in which ferritin is degraded through the NCOA4/HMOX1-dependent pathway [184]. These reactive radicals preferentially target membrane phospholipids containing PUFAs, particularly arachidonic acid and adrenic acid. Several enzymes are critical for the incorporation of PUFAs into membrane phospholipids and thereby determine their susceptibility to peroxidation. These enzymes are tgGNPAT, AGPS, and FAR1 in peroxisomes and ACSL4 and LPCAT3 in the endoplasmic reticulum membrane [185]. High ACSL4 expression is considered one of the strongest molecular predictors of tumor sensitivity to ferroptosis [186].

A mandatory prerequisite for the initiation of ferroptosis is the impairment of cellular antioxidant defenses. To date, several independent but partially overlapping defense systems have been identified that together constitute an integrated ferroptosis defense network [176].

i. The Xc^-–GSH–GPX4 system. The membrane antiporter System Xc^- (SLC7A11/SLC3A2) mediates the uptake of cystine into the cell in exchange for glutamate. Cystine is reduced to cysteine, which is utilized for the synthesis of glutathione (GSH), an essential cofactor for the selenium-containing

enzyme glutathione peroxidase 4 (GPX4). GPX4 catalyzes the reduction of PL-PUFA-OOH to the corresponding relatively non-toxic phospholipid alcohols (PL-PUFA-OH), thereby preventing the initiation and propagation of lipid peroxidation chain reactions [187].

ii. The FSP1–$CoQH_2$ system. Ferroptosis suppressor protein 1 (FSP1; *AIFM2*) is localized predominantly to the cytoplasmic side of the plasma membrane and is also present in the endoplasmic reticulum. Using NADPH as a reducing equivalent, FSP1 reduces ubiquinone (coenzyme Q10, CoQ10) to ubiquinol ($CoQH_2$), a potent lipophilic antioxidant that directly inactivates lipid peroxyl radicals (LOO•) independently of GPX4 and can therefore suppress lipid peroxidation even when GPX4 activity is compromised. The existence of the FSP1–$CoQH_2$ system explains the persistence of cellular resistance to ferroptosis following loss or inactivation of GPX4 [188].

iii. The cyclic GCH1–BH_4–DHFR radical-trapping system. Tetrahydrobiopterin (BH_4) acts as a lipid radical-trapping antioxidant by scavenging lipid peroxyl radicals (LOO•). In addition, the GCH1–BH_4 pathway contributes to the biosynthesis of coenzyme Q and helps preserve polyunsaturated phospholipids in cellular membranes. During BH_4 oxidation, dihydrobiopterin (BH_2) is regenerated to BH_4 by dihydrofolate reductase (DHFR). GCH1 catalyzes BH_4 biosynthesis; its genetic or pharmacological inhibition markedly increases cellular sensitivity to ferroptosis, even in the presence of high GPX4 expression [189]. A related radical-trapping function is provided by the VKORC1L1–vitamin K system [190].

Mitochondria possess their own antioxidant defense system that protects against ferroptosis, centered on the DHODH–$CoQH_2$ pathway [176]. In addition, quinone-reducing enzymes, including NAD(P)H:quinone oxidoreductase 1 (NQO1) and sulfide:quinone oxidoreductase (SQOR) [191, 192], the thioredoxin system (TXN/TXNRD1) [193], and the cellular systems responsible for maintaining the intracellular NADPH pool, a universal source of reducing equivalents for many antiferroptotic mechanisms, contribute to the broader antiferroptotic network [194].

The KEAP1–NRF2 signaling axis is currently considered a major genetic regulator of cellular sensitivity to ferroptosis. Under ferroptotic stress, modification of the repressor protein KEAP1 disrupts its interaction with NRF2, allowing NRF2 to accumulate and translocate to the nucleus, where it activates the transcription of hundreds of cytoprotective genes containing antioxidant response elements (AREs). These genes include several key components of the antiferroptotic defense system described above, such as FSP1, SLC7A11, and GPX4, as well as ferritin subunits FTH1 and FTL, which promote the sequestration of labile Fe^{2+} [195]. Elevated NRF2 activity is thought to be a common mechanism underlying resistance to certain anticancer therapies whose efficacy is mediated through ferroptosis [196].

Therapeutic potential. The metabolic nature of ferroptosis underlies its involvement in several characteristic hallmarks of cancer, including metabolic reprogramming, adaptation to oxidative stress, and evasion of immune surveillance. Malignant cells can reconfigure their metabolism to suppress ferroptosis and maintain viability under the oxidative stress associated with hyperproliferation, hypoxia, and therapeutic exposure [197]. In this respect, ferroptosis differs from other major forms of RCD, such as apoptosis, necroptosis, pyroptosis, and autophagy, as its tumor-suppressive potential is more closely linked to specific metabolic vulnerabilities of malignant cells. This feature has positioned ferroptosis as an important focus for the development of novel therapeutic strategies and targets. Notably, ferroptosis may preferentially eliminate tumor cell populations that evade canonical cell death pathways, including cancer stem cells, metastatic cells that have undergone epithelial–mesenchymal transition, and therapy-resistant persister subpopulations [197, 198]. At the same time, therapeutic induction of ferroptosis must preserve beneficial components of the antitumor immune microenvironment, particularly $CD8^+$ T lymphocytes, NK cells, and dendritic cells [178], while avoiding the recruitment or activation of myeloid-derived suppressor cells and tumor-associated neutrophils [182, 199]. Given the numerous biological variables and potential off-target effects involved, achieving selective and therapeutically effective induction of ferroptosis remains challenging, and its translation into clinical practice is still at an early stage. Nevertheless, substantial progress is being made toward overcoming these barriers.

The first attempts to therapeutically target ferroptotic pathways in cancer are associated with the development of low-molecular-weight ferroptosis inducers (FINs) [175, 200]. These compounds (including erastin, whose use contributed to the discovery of ferroptosis as a distinct form of RCD) suppress the Xc^-–GSH–GPX4 antioxidant system, thereby removing a major barrier to the propagation of lipid peroxidation [201]. However, the clinical application of FINs is limited by their narrow therapeutic window. Because GPX4 and its interacting partners play essential physiological roles in normal tissues, particularly in the kidneys and nervous system, systemic inhibition of this pathway can result in substantial toxicity. The development of more bioavailable and selective FINs, such as RSL3, ML162, and ML210, together with

delivery strategies for tumor-specific drugs, e.g., antibody–drug conjugates and tumor-targeted nanoparticles, represents a major approach to overcoming this limitation [200, 202]. Another promising therapeutic target is FSP1. Several FSP1 inhibitors (iFSP1, icFSP1, viFSP1, and FSEN1) have been developed and shown to enhance ferroptosis *in vitro* and *in vivo*. These compounds have demonstrated antitumor activity in experimental models of melanoma and lung cancer [203, 204].

In any case, the use of ferroptosis inducers as monotherapy is unlikely to have substantial clinical prospects, whereas their combination with other therapeutic interventions represents a promising strategy. This rationale is based on the fact that a major cytotoxic mechanism of conventional chemotherapy and radiotherapy is the generation of ROS, thus inducing oxidative stress and DNA damage in tumor cells. By suppressing the antioxidant defense systems of tumor cells, ferroptosis inducers may potentiate the oxidative damage caused by chemo- and radiotherapy, thereby generating synergistic cytotoxic effects [197]. Moreover, given the distinctive features of lipid metabolism and the increased susceptibility of mesenchymal, stem-like, and "dormant" therapy-resistant cancer cells to ROS-mediated damage, such combinations may help overcome chemo- and radioresistance while delaying tumor progression [11, 205, 206]. Importantly, combining ferroptosis inducers with other therapeutic modalities may also allow for reductions in the doses of individual agents, thereby potentially decreasing treatment-related toxicity [207].

One of the unexpected discoveries in recent years has been the recognition that the lymphatic system can create conditions that protect disseminating tumor cells from ferroptosis. The lymph provides a microenvironment unfavorable to ferroptosis initiation, characterized by high levels of oleic acid and GSH and low concentrations of free iron. These conditions may therefore provide a more permissive route for metastatic colonization by circulating tumor cells than the relatively ferroptosis-prone bloodstream [208, 209]. Experimental attempts to induce ferroptosis and thereby limit the lymphatic dissemination of tumor cells *in vivo* have shown promising results [210].

At present, the combination of FINs with immune checkpoint inhibitors (ICIs) appears to be among the approaches closest to clinical translation. FINs can induce immunogenic ferroptosis, characterized by the release of neoantigens and DAMPs, thereby stimulating adaptive antitumor immunity and potentially converting immunologically "cold" tumors into "hot" tumors [211]. Ferroptosis can also modulate tumor programmed death-ligand 1 (PD-L1) expression through HIF-1α (hypoxia-inducible factor 1 alpha)-dependent mechanisms and reshape the tumor microenvironment, promoting the recruitment of antitumor immune cells [212]. Conversely, ICIs relieve T-cell-mediated immunosuppression and can enhance IFN-γ-dependent ferroptosis, establishing a positive feedback loop between immune activation and ferroptotic cell death [212, 213]. Preclinical studies across multiple tumor models, including triple-negative breast cancer, non-small cell lung cancer, and hepatocellular carcinoma, have demonstrated that combining GPX4 inhibitors or iron chelators with anti-PD-1/PD-L1 antibodies can substantially enhance antitumor efficacy compared with either treatment alone [212].

A promising experimental strategy for exploiting ferroptosis in antitumor therapy involves dietary modulation of the lipid composition of tumor cells. This approach is based on the incorporation of dietary PUFAs into membrane phospholipids, thereby increasing the availability of substrates for lipid peroxidation. Studies in mouse models of KRAS-positive pancreatic cancer have shown that a PUFA-enriched diet can enhance the antitumor activity of ferroptosis inducers. However, the efficacy of this strategy appears to depend on the metabolic characteristics of the tumor and requires further validation [214].

Despite these promising preclinical findings, only a limited number of ferroptosis-based strategies have progressed to clinical trials. Results from a phase Ib/II trial evaluating the combination of the multikinase inhibitor sorafenib, which can promote ferroptosis by interfering with antioxidant defenses, and the ICI pembrolizumab in patients with liver cancer are currently being evaluated (NCT03211416). In another phase I clinical trial, a combination of low-dose radiotherapy and anti-PD-L1 therapy was reported to induce ferroptosis through the Nrf2/HO-1/GPX4 axis and to exert antitumor activity in patients with lung cancer who were resistant to standard chemotherapy and/or immunotherapy regimens [215]. Another combination strategy involving a DDR1/VEGFR2 inhibitor, the ferroptosis inducer K-13, and docetaxel has also demonstrated therapeutic potential in gastric cancer, according to preliminary results from a phase Ib/II clinical trial [216].

CONCLUSION: A NEW INTEGRATIVE PARADIGM OF RCD AS THE BASIS FOR THE DEVELOPMENT OF THERAPEUTIC STRATEGIES

Recent decades have substantially reshaped our understanding of RCD and its role in maintaining homeostasis in both normal and transformed cell populations. In the canonical framework proposed in 2000, evasion of RCD was identified as one of the fundamental hallmarks of cancer [217, 218], a concept

that remains highly relevant today. However, it is now clear that, as the tumor ecosystem evolves, either under unperturbed conditions or in response to therapeutic pressure, RCD pathways can be co-opted to meet the adaptive needs of tumors and thereby lead to consequences detrimental to the patient [219, 220]. The early conceptualization of RCD largely as a synonym for apoptosis as a non-immunogenic form of cell death and as the only alternative to necrosis, provided an important rationale for developing anticancer agents designed to induce apoptosis, exemplified by the BCL-2 inhibitor venetoclax [49]. Although such agents have improved clinical outcomes in specific settings, their therapeutic applicability has proven considerably narrower than initially anticipated [221]. This limitation may, at least in part, reflect an underappreciation of RCD pathways that can function redundantly with apoptosis, as well as of the context-dependent effects of distinct cell death modalities on the tumor microenvironment. These considerations may also help explain a long-standing puzzle in cancer biology, namely, the relative paucity of highly penetrant germline mutations affecting proapoptotic genes among hereditary cancer syndromes, with the notable exception of the multifunctional master regulator *TP53* [222-224].

The concept of independent signaling cascades activated by strictly defined stimuli has increasingly given way to a network model in which apoptosis, necroptosis, autophagy, pyroptosis, ferroptosis, and other forms of RCD form interconnected regulatory networks with multiple switching points. These pathways are closely integrated not only with one another but also with other cellular processes of major oncological relevance [11]. A prominent example of this integrative paradigm is the concept of PANoptosis, whereby specific intracellular sensors and signaling complexes coordinate the molecular machinery of apoptosis, necroptosis, and pyroptosis through the assembly of multiprotein platforms known as PANoptosomes [69, 70]. However, whether PANoptosis represents a distinct form of RCD or rather a coordinated mode of activation involving several established cell death mechanisms remains under debate [225, 226]. This emerging “systems-level” perspective has important therapeutic implications, shifting the focus from the search for universal inducers of individual cell death pathways toward targeting nodal regulatory elements capable of redirecting the cell between alternative death and survival programs according to the clinical context and the evolving state of the tumor. Accordingly, the predictive determinants of treatment efficacy and resistance may lie not in the activity of any single death pathway, but in the overall state and connectivity of the regulatory network governing the cellular survival–death balance [227]. In this context, there is a growing need for next-generation sequencing-based liquid biopsy approaches that enable non-invasive *in vivo* monitoring of RCD pathways before and during targeted therapeutic interventions [228].

One promising direction in modern antitumor therapy involves strategies aimed at exploiting specific vulnerabilities of RCD pathways in specific tumor cell populations, including drug-tolerant cells, infiltrating immune cells, disseminated and dormant tumor cells, circulating metastatic cells, and cancer stem cells [229, 230]. Targeting these populations is considered a key prerequisite for preventing disease relapse and establishing long-term antitumor responses [127, 231].

Importantly, somatic alterations and aberrant expression of genes involved in the regulation and execution of numerous recently identified forms of RCD may represent novel therapeutic targets. However, targeting these abnormalities using monotherapy is unlikely to provide an effective and safe therapeutic strategy. A more promising approach may involve the development of synergistic drug combinations based on the principle of synthetic lethality [232, 233], together with their integration into chemotherapy, targeted therapy, radiotherapy, and immunotherapy regimens [234]. Regardless of a specific RCD pathway being targeted, a major priority is the development of selective drug delivery systems and conjugated therapeutic complexes capable of increasing intratumoral drug concentrations while minimizing systemic toxicity [235].

Abbreviations

DAMP	damage-associated molecular pattern
DISC	death-inducing signaling complex
FSP1	ferroptosis suppressor protein 1
MOMP	mitochondrial outer membrane permeabilization
PAMP	pathogen-associated molecular pattern
PUFA	polyunsaturated fatty acid
RCD	regulated cell death
ROS	reactive oxygen species

Supplementary information

The online version contains supplementary material available at https://doi.org/10.1134/S0006297926603096.

Contributions

E.Sh.K. developed the study concept, and wrote the text of the article, and prepared figures; G.A.Ya. and E.N.I. discussed and edited the manuscript.

Funding

This work was supported by the Russian Science Foundation (project no. 22-15-00278-P).

Ethics approval and consent to participate

This work does not contain any studies involving human or animal subjects.

Conflict of interest

The authors of this work declare that they have no conflicts of interest.

REFERENCES

1. Di, X., et al. (2026) PANoptosis in urological diseases: molecular mechanisms, pathological roles, and emerging therapeutic opportunities, *Front. Immunol.*, **16**, 1729348, https://doi.org/10.3389/fimmu.2025.1729348.
2. Sorokin, O., et al. (2025) Comprehensive analysis of regulated cell death pathways: intrinsic disorder, protein-protein interactions, and cross-pathway communication, *Apoptosis*, **30**, 2110-2162, https://doi.org/10.1007/s10495-025-02161-6.
3. Sender, R., et al. (2021) The distribution of cellular turnover in the human body, *Nat. Med.*, **27**, 45-48, https://doi.org/10.1038/s41591-020-01182-9.
4. Pienta, K. J., et al. (2025) Defeating lethal cancer: interrupting the ecologic and evolutionary basis of death from malignancy, *CA Cancer J. Clin.*, **75**, 183-202, https://doi.org/10.3322/caac.70000.
5. Bergmann, A. (2025) Cell death, compensatory proliferation, and cell competition, *Annu. Rev. Genet.*, **59**, 165-187, https://doi.org/10.1146/annurev-genet-012125-083359.
6. Gao, F., et al. (2024) A PANoptosis pattern to predict prognosis and immunotherapy response in head and neck squamous cell carcinoma, *Heliyon*, **10**, e27162, https://doi.org/10.1016/j.heliyon.2024.e27162.
7. Medina, C. B., et al. (2020) Metabolites released from apoptotic cells act as tissue messengers, *Nature*, **580**, 130-135, https://doi.org/10.1038/s41586-020-2121-3.
8. Saxena, R., et al. (2024) Targeting regulated cell death pathways in cancers for effective treatment: a comprehensive review, *Front. Cell Dev. Biol.*, **12**, 1462339, https://doi.org/10.3389/fcell.2024.1462339.
9. D'Amico, M., et al. (2024) Challenges of regulated cell death: implications for therapy resistance in cancer, *Cells*, **13**, 1083, https://doi.org/10.3390/cells13131083.
10. Tang, D., et al. (2026) Beyond the canon: emerging modalities of regulated cell death, *Cell Death Differ.*, **33**, 1925-1927, https://doi.org/10.1038/s41418-026-01686-w.
11. Conrad, M., et al. (2026) Cell death in cancer, *Cell*, **189**, 2322-2356, https://doi.org/10.1016/j.cell.2026.03.024.
12. Huang, Y., et al. (2024) DAMP sensing and sterile inflammation: intracellular, intercellular and inter-organ pathways, *Nat. Rev. Immunol.*, **24**, 703-719, https://doi.org/10.1038/s41577-024-01027-3.
13. Zhan, B., et al. (2026) Cell death pathways and targeting therapeutics in cancer therapy, *Acta Pharmacol. Sin.*, https://doi.org/10.1038/s41401-026-01803-y.
14. Luo, H., et al. (2026) Regulated cell death programs shaping cancer therapy, *Cell. Oncol. (Dordr.)*, **49**, 102, https://doi.org/10.1007/s13402-026-01232-3.
15. Meng, Y., et al. (2025) Regulated cell death in cancer: mechanisms, crosstalk, and opportunities for therapy, *Cancer Lett.*, **635**, 218077, https://doi.org/10.1016/j.canlet.2025.218077.
16. Galluzzi, L., et al. (2007) Cell death modalities: classification and pathophysiological implications, *Cell Death Differ.*, **14**, 1237-1243, https://doi.org/10.1038/sj.cdd.4402148.
17. Galluzzi, L., et al. (2018) Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018, *Cell Death Differ.*, **25**, 486-541, https://doi.org/10.1038/s41418-017-0012-4.
18. Koltai, T., et al. (2026) Anoikis: to die or not to die? *Int. J. Mol. Sci.*, **27**, 579, https://doi.org/10.3390/ijms27020579.
19. Holze, C., et al. (2018) Oxeiptosis, a ROS-induced caspase-independent apoptosis-like cell-death pathway, *Nat. Immunol.*, **19**, 130-140, https://doi.org/10.1038/s41590-017-0013-y.
20. Tsvetkov, P., et al. (2022) Copper induces cell death by targeting lipoylated TCA cycle proteins, *Science*, **375**, 1254-1261, https://doi.org/10.1126/science.abf0529.
21. Mao, C., et al. (2024) Metabolic cell death in cancer: ferroptosis, cuproptosis, disulfidptosis, and beyond, *Protein Cell*, **15**, 642-660, https://doi.org/10.1093/procel/pwae003.
22. Andrabi, S. A., et al. (2008) Mitochondrial and nuclear cross talk in cell death: parthanatos, *Ann. N. Y. Acad. Sci.*, **1147**, 233-241, https://doi.org/10.1196/annals.1427.014.
23. Lee, H. S., et al. (2026) Zinc-mediated lysosomal destabilization links mitochondrial damage to neuronal death in a cellular MPP+ model of Parkinson's disease, *J. Neurochem.*, **170**, e70363, https://doi.org/10.1111/jnc.70363.
24. Vitale, I., et al. (2023) Apoptotic cell death in disease—current understanding of the NCCD 2023, *Cell Death Differ.*, **30**, 1097-1154, https://doi.org/10.1038/s41418-023-01153-w.
25. Green, D. R. (2022) The mitochondrial pathway of apoptosis part II: the BCL-2 protein family, *Cold Spring Harb. Perspect. Biol.*, **14**, a041046, https://doi.org/10.1101/cshperspect.a041046.
26. Vogler, M., et al. (2025) The BCL2 family: from apoptosis mechanisms to new advances in targeted therapy, *Signal Transduct. Target. Ther.*, **10**, 91, https://doi.org/10.1038/s41392-025-02176-0.

27. Green, D. R. (2022) The mitochondrial pathway of apoptosis: part I: MOMP and beyond, *Cold Spring Harb. Perspect. Biol.*, **14**, a041038, https://doi.org/10.1101/cshperspect.a041038.
28. Croce, C. M., et al. (2025) The BCL-2 protein family: from discovery to drug development, *Cell Death Differ.*, **32**, 1369-1381, https://doi.org/10.1038/s41418-025-01481-z.
29. Liu, Y., et al. (2019) p53 modifications: exquisite decorations of the powerful guardian, *J. Mol. Cell Biol.*, **11**, 564-577, https://doi.org/10.1093/jmcb/mjz060.
30. Schuler, M., et al. (2003) p53 triggers apoptosis in oncogene-expressing fibroblasts by the induction of Noxa and mitochondrial Bax translocation, *Cell Death Differ.*, **10**, 451-460, https://doi.org/10.1038/sj.cdd.4401180.
31. Hao, Q., et al. (2023) The ARTS of p53-dependent mitochondrial apoptosis, *J. Mol. Cell Biol.*, **14**, mjac074, https://doi.org/10.1093/jmcb/mjac074.
32. Kowalczyk, D., et al. (2022) Bivalent binding of p14ARF to MDM2 RING and acidic domains inhibits E3 ligase function, *Life Sci. Alliance*, **5**, e202201472, https://doi.org/10.26508/lsa.202201472.
33. Green, D. R. (2022) Cell death and cancer, *Cold Spring Harb. Perspect. Biol.*, **14**, a041103, https://doi.org/10.1101/cshperspect.a041103.
34. Kalkavan, H., et al. (2022) Sublethal cytochrome c release generates drug-tolerant persister cells, *Cell*, **185**, 3356-3374.e22, https://doi.org/10.1016/j.cell.2022.07.025.
35. Huang, P., et al. (2022) Molecular mechanisms of parthanatos and its role in diverse diseases, *Int. J. Mol. Sci.*, **23**, 7292, https://doi.org/10.3390/ijms23137292.
36. Gupta, G., et al. (2025) Parthanatos and apoptosis: unraveling their roles in cancer cell death and therapy resistance, *EXCLI J.*, **24**, 351-380, https://doi.org/10.17179/excli2025-8251.
37. Green, D. R. (2022) The death receptor pathway of apoptosis, *Cold Spring Harb. Perspect. Biol.*, **14**, a041053, https://doi.org/10.1101/cshperspect.a041053.
38. Brisset, M., et al. (2021) Dependence receptors: new targets for cancer therapy, *EMBO Mol. Med.*, **13**, e14495, https://doi.org/10.15252/emmm.202114495.
39. Horn, S., et al. (2017) Caspase-10 negatively regulates caspase-8-mediated cell death, switching the response to CD95L in favor of NF-κB activation and cell survival, *Cell Rep.*, **19**, 785-797, https://doi.org/10.1016/j.celrep.2017.04.010.
40. Ozören, N., et al. (2002) Defining characteristics of types I and II apoptotic cells in response to TRAIL, *Neoplasia*, **4**, 551-557, https://doi.org/10.1038/sj.neo.7900270.
41. Lamkanfi, M., et al. (2026) Comparative insights into the apoptosome, inflammasomes and PIDDosome, *Nat. Rev. Immunol.*, **26**, 729-744, https://doi.org/10.1038/s41577-026-01304-3.
42. Li, G., et al. (2025) Efferocytosis: the art of cellular clearance and novel perspectives in disease therapy, *Mol. Cancer*, **24**, 268, https://doi.org/10.1186/s12943-025-02484-7.
43. Zhou, L., et al. (2025) The battle within: cell death by phagocytosis in cancer, *Clin. Transl. Oncol.*, **27**, 871-886, https://doi.org/10.1007/s12094-024-03650-x.
44. Liu, J., et al. (2019) Induction of entosis in prostate cancer cells by nintedanib and its therapeutic implications, *Oncol. Lett.*, **17**, 3151-3162, https://doi.org/10.3892/ol.2019.9951.
45. Kim, S., et al. (2024) Entosis: the core mechanism and crosstalk with other cell death programs, *Exp. Mol. Med.*, **56**, 870-876, https://doi.org/10.1038/s12276-024-01227-w.
46. Liang, J., et al. (2021) p53-dependent elimination of aneuploid mitotic offspring by entosis, *Cell Death Differ.*, **28**, 799-813, https://doi.org/10.1038/s41418-020-00645-3.
47. Borensztejn, K., et al. (2021) Classification of cell-in-cell structures: different phenomena with similar appearance, *Cells*, **10**, 2569, https://doi.org/10.3390/cells10102569.
48. Bozkurt, E., et al. (2026) Cell engulfment defines spatially distinct competitive metabolic niches associated with clinical outcomes in colorectal cancer, *Cell Death Differ.*, https://doi.org/10.1038/s41418-026-01801-x.
49. Anderson, M. A., et al. (2016) The BCL2 selective inhibitor venetoclax induces rapid onset apoptosis of CLL cells in patients via a TP53-independent mechanism, *Blood*, **127**, 3215-3224, https://doi.org/10.1182/blood-2016-01-688796.
50. Al-Sawaf, O., et al. (2023) Transcriptomic profiles and 5-year results from the randomized CLL14 study of venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab in chronic lymphocytic leukemia, *Nat. Commun.*, **14**, 2147, https://doi.org/10.1038/s41467-023-37648-w.
51. Pratz, K. W., et al. (2024) Long-term follow-up of VIALE-A: venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia, *Am. J. Hematol.*, **99**, 615-624, https://doi.org/10.1002/ajh.27246.
52. Kumar, S. K., et al. (2020) Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial, *Lancet Oncol.*, **21**, 1630-1642, https://doi.org/10.1016/S1470-2045(20)30525-8.

53. Wang, Z., et al. (2026) Anti-apoptotic BCL-2 family proteins: from regulatory networks to therapeutic targeting, *Oncogenesis*, **15**, 43, https://doi.org/10.1038/s41389-026-00632-2.
54. Blair, H. A. (2026) Sonrotoclax: first approval, *Drugs*, **86**, 1153-1163, https://doi.org/10.1007/s40265-026-02322-0.
55. Smith, V. M., et al. (2020) Specific interactions of BCL-2 family proteins mediate sensitivity to BH3-mimetics in diffuse large B-cell lymphoma, *Haematologica*, **105**, 2150-2163, https://doi.org/10.3324/haematol.2019.220525.
56. Lasater, E. A., et al. (2023) Targeting MCL-1 and BCL-2 with polatuzumab vedotin and venetoclax overcomes treatment resistance in R/R non-Hodgkin lymphoma: results from preclinical models and a phase Ib study, *Am. J. Hematol.*, **98**, 449-463, https://doi.org/10.1002/ajh.26809.
57. Morschhauser, F., et al. (2021) A phase 2 study of venetoclax plus R-CHOP as first-line treatment for patients with diffuse large B-cell lymphoma, *Blood*, **137**, 600-609, https://doi.org/10.1182/blood.2020006578.
58. Schmitt, N. C., et al. (2025) Early-phase trial of IAP antagonist tolinapant and definitive radiation in cisplatin-ineligible patients with advanced head and neck cancer, *Clin. Cancer Res.*, **31**, 2910-2918, https://doi.org/10.1158/1078-0432.CCR-25-0429.
59. Huang, X., et al. (2026) Apoptosis signaling and cancer targeted therapy: from bench to bespoke, *Transl. Cancer Res.*, **15**, 435, https://doi.org/10.21037/tcr-2026-1-0243.
60. Bourhis, J., et al. (2025) Xevinapant or placebo plus platinum-based chemoradiotherapy in unresected locally advanced squamous cell carcinoma of the head and neck (TrilynX): a randomized, phase III study, *J. Clin. Oncol.*, **43**, 3209-3220, https://doi.org/10.1200/JCO-25-00272.
61. Montinaro, A., et al. (2023) Harnessing TRAIL-induced cell death for cancer therapy: a long walk with thrilling discoveries, *Cell Death Differ.*, **30**, 237-249, https://doi.org/10.1038/s41418-022-01059-z.
62. Wang, W., et al. (2024) MDM2 inhibitors for cancer therapy: the past, present, and future, *Pharmacol. Rev.*, **76**, 414-453, https://doi.org/10.1124/pharmrev.123.001026.
63. Sallman, D. A., et al. (2025) TP53-mutated acute myeloid leukemia: how can we improve outcomes? *Blood*, **145**, 2828-2833, https://doi.org/10.1182/blood.2024024245.
64. Laster, S. M., et al. (1988) Tumor necrosis factor can induce both apoptic and necrotic forms of cell lysis, *J. Immunol.*, **141**, 2629-2634.
65. Zhang, C., et al. (2026) Unleashing necroptosis: transforming the tumor immune microenvironment for cancer therapy, *Biomed. Pharmacother.*, **195**, 118988, https://doi.org/10.1016/j.biopha.2026.118988.
66. Noh, H., et al. (2026) SIGLEC12 mediates plasma membrane rupture during necroptotic cell death, *Nature*, **649**, 460-466, https://doi.org/10.1038/s41586-025-09741-1.
67. Zhang, Z., et al. (2024) Induced necroptosis and its role in cancer immunotherapy, *Int. J. Mol. Sci.*, **25**, 10760, https://doi.org/10.3390/ijms251910760.
68. Frank, T., et al. (2019) Cell cycle arrest in mitosis promotes interferon-induced necroptosis, *Cell Death Differ.*, **26**, 2046-2060, https://doi.org/10.1038/s41418-019-0298-5.
69. Yao, L., et al. (2026) When death pathways converge: PANoptosis in the evolution and treatment of female tumors, *Crit. Rev. Oncol. Hematol.*, **224**, 105380, https://doi.org/10.1016/j.critrevonc.2026.105380.
70. Pu, X., et al. (2025) PANoptosis in cancer: molecular mechanisms and therapeutic potential, *Cancer Gene Ther.*, **32**, 1042-1053, https://doi.org/10.1038/s41417-025-00940-6.
71. Sharma, B. R., et al. (2023) Immune regulator IRF1 contributes to ZBP1-, AIM2-, RIPK1-, and NLRP12-PANoptosome activation and inflammatory cell death (PANoptosis), *J. Biol. Chem.*, **299**, 105141, https://doi.org/10.1016/j.jbc.2023.105141.
72. Ma, W., et al. (2025) The molecular mechanisms, roles, and potential applications of PANoptosis in cancer treatment, *Front. Immunol.*, **16**, 1550800, https://doi.org/10.3389/fimmu.2025.1550800.
73. Zengeler, K. E., et al. (2026) PANoptosis in life and death across cell types: from innate immunity to therapeutic implications, *Cell Chem. Biol.*, **33**, 1021-1037, https://doi.org/10.1016/j.chembiol.2026.06.007.
74. De Duve, C., et al. (1966) Functions of lysosomes, *Annu. Rev. Physiol.*, **28**, 435-492, https://doi.org/10.1146/annurev.ph.28.030166.002251.
75. Guilbaud, E., et al. (2026) Autophagy modulation in cancer, *Nat. Rev. Drug Discov.*, **25**, 701-722, https://doi.org/10.1038/s41573-026-01449-9.
76. Ryter, S. W., et al. (2019) Autophagy: a lysosome-dependent process with implications in cellular redox homeostasis and human disease, *Antioxid. Redox Signal.*, **30**, 138-159, https://doi.org/10.1089/ars.2018.7518.
77. Gómez-Virgilio, L., et al. (2022) Autophagy: a key regulator of homeostasis and disease: an overview of molecular mechanisms and modulators, *Cells*, **11**, 2262, https://doi.org/10.3390/cells11152262.
78. Katheder, N. S., et al. (2017) Microenvironmental autophagy promotes tumour growth, *Nature*, **541**, 417-420, https://doi.org/10.1038/nature20815.

79. He, J., et al. (2026) Autophagy: mechanisms, roles in human diseases, and therapeutic perspectives, *Front. Cell Dev. Biol.*, **14**, 1776289, https://doi.org/10.3389/fcell.2026.1776289.
80. Liu, J., et al. (2024) Selective autophagy in cancer: mechanisms, therapeutic implications, and future perspectives, *Mol. Cancer*, **23**, 22, https://doi.org/10.1186/s12943-024-01934-y.
81. Ma, W., et al. (2024) Targeting selective autophagy and beyond: from underlying mechanisms to potential therapies, *J. Adv. Res.*, **65**, 297-327, https://doi.org/10.1016/j.jare.2024.05.009.
82. Galluzzi, L., et al. (2015) Autophagy in malignant transformation and cancer progression, *EMBO J.*, **34**, 856-880, https://doi.org/10.15252/embj.201490784.
83. Eskelinen, E. L. (2011) The dual role of autophagy in cancer, *Curr. Opin. Pharmacol.*, **11**, 294-300, https://doi.org/10.1016/j.coph.2011.03.009.
84. Ayub, A., et al. (2024) Dissecting the multifaceted roles of autophagy in cancer initiation, growth, and metastasis: from molecular mechanisms to therapeutic applications, *Med. Oncol.*, **41**, 183, https://doi.org/10.1007/s12032-024-02417-2.
85. Patergnani, S., et al. (2021) Understanding the role of autophagy in cancer formation and progression is a real opportunity to treat and cure human cancers, *Cancers (Basel)*, **13**, 5622, https://doi.org/10.3390/cancers13225622.
86. Yamamoto, K., et al. (2020) Autophagy promotes immune evasion of pancreatic cancer by degrading MHC-I, *Nature*, **581**, 100-105, https://doi.org/10.1038/s41586-020-2229-5.
87. Xia, H., et al. (2021) Autophagy in tumour immunity and therapy, *Nat. Rev. Cancer*, **21**, 281-297, https://doi.org/10.1038/s41568-021-00344-2.
88. Jiang, T., et al. (2021) Emerging role of autophagy in anti-tumor immunity: implications for the modulation of immunotherapy resistance, *Drug Resist. Updat.*, **56**, 100752, https://doi.org/10.1016/j.drup.2021.100752.
89. Hurley, J. H. (2026) The human autophagy core complexes, *Annu. Rev. Biochem.*, **95**, 507-524, https://doi.org/10.1146/annurev-biochem-072425-030036.
90. Lu, G., et al. (2022) Autophagy in health and disease: from molecular mechanisms to therapeutic target, *MedComm*, **3**, e150, https://doi.org/10.1002/mco2.150.
91. Li, X., et al. (2020) Autophagy and autophagy-related proteins in cancer, *Mol. Cancer*, **19**, 12, https://doi.org/10.1186/s12943-020-1138-4.
92. Chen, M., et al. (2025) The human autophagy-initiating complexes ULK1C and PI3KC3-C1, *J. Biol. Chem.*, **301**, 110391, https://doi.org/10.1016/j.jbc.2025.110391.
93. Russell, R. C., et al. (2013) ULK1 induces autophagy by phosphorylating Beclin-1 and activating VPS34 lipid kinase, *Nat. Cell Biol.*, **15**, 741-750, https://doi.org/10.1038/ncb2757.
94. Liu, H., et al. (2026) Integrating the hallmarks of cancer into autophagy: a perspective from underlying mechanisms to therapeutic strategies, *Theranostics*, **16**, 6948-6979, https://doi.org/10.7150/thno.135134.
95. Jian, F., et al. (2024) The STX17-SNAP47-VAMP7/VAMP8 complex is the default SNARE complex mediating autophagosome-lysosome fusion, *Cell Res.*, **34**, 151-168, https://doi.org/10.1038/s41422-023-00916-x.
96. Selarka, K., et al. (2024) Illuminating intercellular autophagy: a comprehensive review of cell non-autonomous autophagy, *Biochem. Biophys. Res. Commun.*, **716**, 150024, https://doi.org/10.1016/j.bbrc.2024.150024.
97. Chen, X., et al. (2024) International consensus guidelines for the definition, detection, and interpretation of autophagy-dependent ferroptosis, *Autophagy*, **20**, 1213-1246, https://doi.org/10.1080/15548627.2024.2319901.
98. Zhou, Y., et al. (2021) Parthanatos and its associated components: promising therapeutic targets for cancer, *Pharmacol. Res.*, **163**, 105299, https://doi.org/10.1016/j.phrs.2020.105299.
99. Nikoletopoulou, V., et al. (2013) Crosstalk between apoptosis, necrosis and autophagy, *Biochim. Biophys. Acta*, **1833**, 3448-3459, https://doi.org/10.1016/j.bbamcr.2013.06.001.
100. Liu, Y., et al. (2025) p53-regulated non-apoptotic cell death pathways and their relevance in cancer and other diseases, *Nat. Rev. Mol. Cell Biol.*, **26**, 600-614, https://doi.org/10.1038/s41580-025-00842-3.
101. Shi, K., et al. (2020) p53 controls the switch between autophagy and apoptosis through regulation of PLSCR1 in sodium selenite-treated leukemia cells, *Exp. Cell Res.*, **389**, 111879, https://doi.org/10.1016/j.yexcr.2020.111879.
102. Goodall, M. L., et al. (2016) The autophagy machinery controls cell death switching between apoptosis and necroptosis, *Dev. Cell*, **37**, 337-349, https://doi.org/10.1016/j.devcel.2016.04.018.
103. Zając, A., et al. (2023) The role of Bcl-2 and Beclin-1 complex in "switching" between apoptosis and autophagy in human glioma cells upon LY294002 and sorafenib treatment, *Cells*, **12**, 2670, https://doi.org/10.3390/cells12232670.
104. Wan, W. D., et al. (2026) Metabolism, autophagy, and cell death: the triangular axis in tumor survival and therapeutic resistance, *Redox Biol.*, **95**, 104269, https://doi.org/10.1016/j.redox.2026.104269.
105. Nagakannan, P., et al. (2025) TXNIP promotes ferroptosis through NCOA4 mediated ferritinophagy, *Biochim. Biophys. Acta Mol. Cell Res.*, **1872**, 120054, https://doi.org/10.1016/j.bbamcr.2025.120054.

106. Sokołowski, M., et al. (2025) Trigger points of necroptosis (RIPK1, RIPK3, and MLKL)—promising horizon or blind alley in therapy of colorectal cancer? *Int. J. Mol. Sci.*, **26**, 11101, https://doi.org/10.3390/ijms262211101.
107. Daskalaki, I., et al. (2018) Hypoxia and selective autophagy in cancer development and therapy, *Front. Cell Dev. Biol.*, **6**, 104, https://doi.org/10.3389/fcell.2018.00104.
108. Yu, Y. S., et al. (2025) Decoding the dual role of autophagy in cancer through transcriptional and epigenetic regulation, *FEBS Lett.*, **599**, 2237-2249, https://doi.org/10.1002/1873-3468.70060.
109. Pimentel, J. M., et al. (2024) Autophagy and cancer therapy, *Cancer Lett.*, **605**, 217285, https://doi.org/10.1016/j.canlet.2024.217285.
110. Li, X., et al. (2010) The epidermal growth factor receptor antibody cetuximab induces autophagy in cancer cells by downregulating HIF-1alpha and Bcl-2 and activating the beclin 1/hVps34 complex, *Cancer Res.*, **70**, 5942-5952, https://doi.org/10.1158/0008-5472.CAN-10-0157.
111. Wei, Y., et al. (2013) EGFR-mediated Beclin 1 phosphorylation in autophagy suppression, tumor progression, and tumor chemoresistance, *Cell*, **154**, 1269-1284, https://doi.org/10.1016/j.cell.2013.08.015.
112. Xu, R., et al. (2016) MicroRNA-30a downregulation contributes to chemoresistance of osteosarcoma cells through activating Beclin-1-mediated autophagy, *Oncol. Rep.*, **35**, 1757-1763, https://doi.org/10.3892/or.2015.4497.
113. Kumar, A., et al. (2023) Targeting autophagy using long non-coding RNAs (lncRNAs): new landscapes in the arena of cancer therapeutics, *Cells*, **12**, 810, https://doi.org/10.3390/cells12050810.
114. Bahar, E., et al. (2022) Chemotherapy resistance: role of mitochondrial and autophagic components, *Cancers (Basel)*, **14**, 1462, https://doi.org/10.3390/cancers14061462.
115. Lei, Y., et al. (2022) The microRNA-based strategies to combat cancer chemoresistance via regulating autophagy, *Front. Oncol.*, **12**, 841625, https://doi.org/10.3389/fonc.2022.841625.
116. Luo, M., et al. (2018) miR-216b enhances the efficacy of vemurafenib by targeting Beclin-1, UVRAG and ATG5 in melanoma, *Cell Signal.*, **42**, 30-43, https://doi.org/10.1016/j.cellsig.2017.09.024.
117. Raghavendra, A. S., et al. (2025) Phase I trial of hydroxychloroquine to enhance palbociclib and letrozole efficacy in ER+/HER2- breast cancer, *NPJ Breast Cancer*, **11**, 7, https://doi.org/10.1038/s41523-025-00722-1.
118. Halcrow, P. W., et al. (2021) Overcoming chemoresistance: altering pH of cellular compartments by chloroquine and hydroxychloroquine, *Front. Cell Dev. Biol.*, **9**, 627639, https://doi.org/10.3389/fcell.2021.627639.
119. Abdel Karim, N., et al. (2025) A phase I trial to determine the safety and tolerability of autophagy inhibition using chloroquine or hydroxychloroquine in combination with carboplatin and gemcitabine in patients with advanced solid tumors, *Asian Pac. J. Cancer Prev.*, **26**, 1165-1172, https://doi.org/10.31557/APJCP.2025.26.4.1165.
120. Xu, R., et al. (2018) The clinical value of using chloroquine or hydroxychloroquine as autophagy inhibitors in the treatment of cancers: a systematic review and meta-analysis, *Medicine (Baltimore)*, **97**, e12912, https://doi.org/10.1097/MD.0000000000012912.
121. Mohiuddin, M., et al. (2026) Autophagy modulation in cancer therapy: navigating the dual roles to overcome chemoresistance, *Health Sci. Rep.*, **9**, e72910, https://doi.org/10.1002/hsr2.72910.
122. Chicote, J., et al. (2020) Cell death triggered by the autophagy inhibitory drug 3-methyladenine in growing conditions proceeds with DNA damage, *Front. Pharmacol.*, **11**, 580343, https://doi.org/10.3389/fphar.2020.580343.
123. Demetri, G. D., et al. (2013) Results of an international randomized phase III trial of the mammalian target of rapamycin inhibitor ridaforolimus versus placebo to control metastatic sarcomas in patients after benefit from prior chemotherapy, *J. Clin. Oncol.*, **31**, 2485-2492, https://doi.org/10.1200/JCO.2012.45.5766.
124. Senapati, P. K., et al. (2025) mTOR inhibitors in targeting autophagy and autophagy-associated signaling for cancer cell death and therapy, *Biochim. Biophys. Acta Rev. Cancer*, **1880**, 189342, https://doi.org/10.1016/j.bbcan.2025.189342.
125. Kwitkowski, V. E., et al. (2010) FDA approval summary: temsirolimus as treatment for advanced renal cell carcinoma, *Oncologist*, **15**, 428-435, https://doi.org/10.1634/theoncologist.2009-0178.
126. Wang, W., et al. (2023) Curcumin in cancer therapy: exploring molecular mechanisms and overcoming clinical challenges, *Cancer Lett.*, **570**, 216332, https://doi.org/10.1016/j.canlet.2023.216332.
127. DeMichele, A., et al. (2025) Targeting dormant tumor cells to prevent recurrent breast cancer: a randomized phase 2 trial, *Nat. Med.*, **31**, 3464-3474, https://doi.org/10.1038/s41591-025-03877-3.
128. Almutairi, J. A. (2025) Targeting autophagy to enhance cancer immunotherapy: emerging mechanisms and strategies, *Med. Oncol.*, **42**, 520, https://doi.org/10.1007/s12032-025-03081-w.
129. Johnson, D. E., et al. (2025) Triggering pyroptosis in cancer, *Biomolecules*, **15**, 348, https://doi.org/10.3390/biom15030348.
130. Liu, Y., et al. (2024) Pyroptosis in health and disease: mechanisms, regulation and clinical perspective, *Signal Transduct. Target. Ther.*, **9**, 245, https://doi.org/10.1038/s41392-024-01958-2.
131. Hu, M., et al. (2024) The crosstalk between immune cells and tumor pyroptosis: advancing cancer immunotherapy strategies, *J. Exp. Clin. Cancer Res.*, **43**, 190, https://doi.org/10.1186/s13046-024-03115-7.

132. Bergsbaken, T., et al. (2009) Pyroptosis: host cell death and inflammation, *Nat. Rev. Microbiol.*, **7**, 99-109, https://doi.org/10.1038/nrmicro2070.
133. Shi, J., et al. (2015) Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death, *Nature*, **526**, 660-665, https://doi.org/10.1038/nature15514.
134. Zhong, X., et al. (2023) Structural mechanisms for regulation of GSDMB pore-forming activity, *Nature*, **616**, 598-605, https://doi.org/10.1038/s41586-023-05872-5.
135. Huston, H. C., et al. (2023) Pyroptosis and the cellular consequences of gasdermin pores, *Semin. Immunol.*, **69**, 101803, https://doi.org/10.1016/j.smim.2023.101803.
136. Li, D., et al. (2021) Pattern recognition receptors in health and diseases, *Signal Transduct. Target. Ther.*, **6**, 291, https://doi.org/10.1038/s41392-021-00687-0.
137. Alishvandi, A., et al. (2025) Pyroptosis in cancer therapy: a double-edged sword for immune activation and tumor progression, *Mol. Cancer*, **24**, 297, https://doi.org/10.1186/s12943-025-02506-4.
138. Xia, S., et al. (2020) Mechanism and regulation of gasdermin-mediated cell death, *Cold Spring Harb. Perspect. Biol.*, **12**, a036400, https://doi.org/10.1101/cshperspect.a036400.
139. Zhao, Y., et al. (2018) Inflammatory caspases: activation and cleavage of gasdermin-D in vitro and during pyroptosis, *Methods Mol. Biol.*, **1714**, 131-148, https://doi.org/10.1007/978-1-4939-7519-8_9.
140. Zhang, Z., et al. (2026) Pyroptosis: turning up the heat on cancer, *Annu. Rev. Immunol.*, **44**, 295-323, https://doi.org/10.1146/annurev-immunol-082423-041848.
141. Jiang, M., et al. (2020) The caspase-3/GSDME signal pathway as a switch between apoptosis and pyroptosis in cancer, *Cell Death Discov.*, **6**, 112, https://doi.org/10.1038/s41420-020-00349-0.
142. Zhou, Z., et al. (2020) Granzyme A from cytotoxic lymphocytes cleaves GSDMB to trigger pyroptosis in target cells, *Science*, **368**, eaaz7548, https://doi.org/10.1126/science.aaz7548.
143. Zhang, Z., et al. (2020) Gasdermin E suppresses tumour growth by activating anti-tumour immunity, *Nature*, **579**, 415-420, https://doi.org/10.1038/s41586-020-2071-9.
144. Li, L., et al. (2021) Pyroptosis, a new bridge to tumor immunity, *Cancer Sci.*, **112**, 3979-3994, https://doi.org/10.1111/cas.15059.
145. Singh, V., et al. (2025) Role of inflammasomes in cancer immunity: mechanisms and therapeutic potential, *J. Exp. Clin. Cancer Res.*, **44**, 109, https://doi.org/10.1186/s13046-025-03366-y.
146. Evavold, C. L., et al. (2018) How inflammasomes inform adaptive immunity, *J. Mol. Biol.*, **430**, 217-237, https://doi.org/10.1016/j.jmb.2017.09.019.
147. Ouyang, X., et al. (2023) Pyroptosis, inflammasome, and gasdermins in tumor immunity, *Innate Immun.*, **29**, 3-13, https://doi.org/10.1177/17534259221143216.
148. Yang, W., et al. (2022) Pyroptosis impacts the prognosis and treatment response in gastric cancer via immune system modulation, *Am. J. Cancer Res.*, **12**, 1511-1534.
149. Triantafillidis, J. K. (2026) The paradoxical role of pyroptosis in gastrointestinal cancers: from molecular mechanisms to therapeutic horizons, *Biomedicines*, **14**, 911, https://doi.org/10.3390/biomedicines14040911.
150. Gao, H., et al. (2025) Caspase-6/gasdermin C-mediated tumor cell pyroptosis promotes colorectal cancer progression through CXCL2-dependent recruitment of myeloid-derived suppressor cells, *Adv. Sci. (Weinh.)*, **12**, e2411375, https://doi.org/10.1002/advs.202411375.
151. Meyer, C., et al. (2011) Chronic inflammation promotes myeloid-derived suppressor cell activation blocking antitumor immunity in transgenic mouse melanoma model, *Proc. Natl. Acad. Sci. USA*, **108**, 17111-17116, https://doi.org/10.1073/pnas.1108121108.
152. Lu, L., et al. (2020) IL-1β promotes stemness of tumor cells by activating Smad/ID1 signaling pathway, *Int. J. Med. Sci.*, **17**, 1257-1268, https://doi.org/10.7150/ijms.44285.
153. Zhao, Q., et al. (2022) The central role of a two-way positive feedback pathway in molecular targeted therapies-mediated pyroptosis in anaplastic thyroid cancer, *Clin. Transl. Med.*, **12**, e727, https://doi.org/10.1002/ctm2.727.
154. Rizkallah, J., et al. (2025) Melittin-based nanoparticles for cancer therapy: mechanisms, applications, and future perspectives, *Pharmaceutics*, **17**, 1019, https://doi.org/10.3390/pharmaceutics17081019.
155. Shen, X., et al. (2021) Caspase 3/GSDME-dependent pyroptosis contributes to chemotherapy drug-induced nephrotoxicity, *Cell Death Dis.*, **12**, 186, https://doi.org/10.1038/s41419-021-03458-5.
156. Han, E., et al. (2023) Development of polymersomes co-delivering doxorubicin and melittin to overcome multidrug resistance, *Molecules*, **28**, 1087, https://doi.org/10.3390/molecules28031087.
157. Zhao, L., et al. (2024) Nanoparticle-mediated cell pyroptosis: a new therapeutic strategy for inflammatory diseases and cancer, *J. Nanobiotechnology*, **22**, 504, https://doi.org/10.1186/s12951-024-02763-3.
158. Wang, Z., et al. (2024) Nanomaterial-induced pyroptosis: a cell type-specific perspective, *Front. Cell Dev. Biol.*, **11**, 1322305, https://doi.org/10.3389/fcell.2023.1322305.

159. Bao, X., et al. (2024) Applications of pyroptosis activators in tumor immunotherapy, *Mater. Today Bio*, **28**, 101191, https://doi.org/10.1016/j.mtbio.2024.101191.
160. Wu, D., et al. (2021) Cell death mediated by the pyroptosis pathway with the aid of nanotechnology: prospects for cancer therapy, *Angew. Chem. Int. Ed. Engl.*, **60**, 8018-8034, https://doi.org/10.1002/anie.202010281.
161. Tian, L., et al. (2025) Functional materials targeted regulation of gasdermins: from fundamentals to functionalities and applications, *Adv. Sci. (Weinh.)*, **12**, e2500873, https://doi.org/10.1002/advs.202500873.
162. Yuan, Z., et al. (2025) 5-FU@HFn combined with decitabine induces pyroptosis and enhances antitumor immunotherapy for chronic myeloid leukemia, *J. Nanobiotechnology*, **23**, 252, https://doi.org/10.1186/s12951-025-03335-9.
163. Yu, X., et al. (2023) Neutrophil camouflaged stealth nanovehicle for photothermal-induced tumor immunotherapy by triggering pyroptosis, *Adv. Sci. (Weinh.)*, **10**, e2207456, https://doi.org/10.1002/advs.202207456.
164. Yang, J., et al. (2023) Self-assembled albumin nanoparticles induce pyroptosis for photodynamic/photothermal/immuno synergistic therapies in triple-negative breast cancer, *Front. Immunol.*, **14**, 1173487, https://doi.org/10.3389/fimmu.2023.1173487.
165. Huang, K. C.-Y., et al. (2020) Decitabine augments chemotherapy-induced PD-L1 upregulation for PD-L1 blockade in colorectal cancer, *Cancers (Basel)*, **12**, 462, https://doi.org/10.3390/cancers12020462.
166. Liu, Y., et al. (2020) Gasdermin E-mediated target cell pyroptosis by CAR T cells triggers cytokine release syndrome, *Sci. Immunol.*, **5**, eaax7969, https://doi.org/10.1126/sciimmunol.aax7969.
167. Zhang, Y., et al. (2023) Exploring CAR-T cell therapy side effects: mechanisms and management strategies, *J. Clin. Med.*, **12**, 6124, https://doi.org/10.3390/jcm12196124.
168. Deng, T., et al. (2021) DAMPs released by pyroptotic cells as major contributors and therapeutic targets for CAR-T-related toxicities, *Cell Death Dis.*, **12**, 129, https://doi.org/10.1038/s41419-021-03428-x.
169. Wang, S., et al. (2024) Gasdermin C sensitizes tumor cells to PARP inhibitor therapy in cancer models, *J. Clin. Invest.*, **134**, e166841, https://doi.org/10.1172/JCI166841.
170. Xia, Y., et al. (2024) PARP inhibitors enhance antitumor immune responses by triggering pyroptosis via TNF-caspase 8-GSDMD/E axis in ovarian cancer, *J. Immunother. Cancer*, **12**, e009032, https://doi.org/10.1136/jitc-2024-009032.
171. Kim, C., et al. (2023) PARP1 inhibitors induce pyroptosis via caspase 3-mediated gasdermin E cleavage, *Biochem. Biophys. Res. Commun.*, **646**, 78-85, https://doi.org/10.1016/j.bbrc.2023.01.055.
172. Tian, A., et al. (2023) Triggering pyroptosis enhances the antitumor efficacy of PARP inhibitors in prostate cancer, *Cell. Oncol. (Dordr.)*, **46**, 1855-1870, https://doi.org/10.1007/s13402-023-00860-3.
173. Huang, C., et al. (2025) Targeting pyroptosis for cancer immunotherapy: mechanistic insights and clinical perspectives, *Mol. Cancer*, **24**, 131, https://doi.org/10.1186/s12943-025-02344-4.
174. Yin, Q., et al. (2024) Unlocking the potential of pyroptosis in tumor immunotherapy: a new horizon in cancer treatment, *Front. Immunol.*, **15**, 1381778, https://doi.org/10.3389/fimmu.2024.1381778.
175. Dixon, S. J., et al. (2012) Ferroptosis: an iron-dependent form of nonapoptotic cell death, *Cell*, **149**, 1060-1072, https://doi.org/10.1016/j.cell.2012.03.042.
176. Duo, K., et al. (2025) Ferroptosis inhibitors: mechanisms of action and therapeutic potential, *Cell. Mol. Life Sci.*, **82**, 441, https://doi.org/10.1007/s00018-025-05958-5.
177. Xu, Q., et al. (2025) The role of ferroptosis in women's health and diseases, *MedComm*, **6**, e70296, https://doi.org/10.1002/mco2.70296.
178. Lei, G., et al. (2024) The roles of ferroptosis in cancer: tumor suppression, tumor microenvironment, and therapeutic interventions, *Cancer Cell*, **42**, 513-534, https://doi.org/10.1016/j.ccell.2024.03.011.
179. Zhang, M., et al. (2026) The role of ferroptosis in the pathogenesis and treatment of breast cancer, *J. Transl. Med.*, **24**, 1138, https://doi.org/10.1186/s12967-026-08594-0.
180. Kumari, R., et al. (2026) Distinct molecular pathways driving lung cancer in non-smokers: etiology, signaling networks, and clinical implications, *Crit. Rev. Oncol. Hematol.*, **226**, 105436, https://doi.org/10.1016/j.critrevonc.2026.105436.
181. Ji, S., et al. (2026) FOXO3/HMOX1 axis promotes melanoma progression by regulating ferroptosis and immune escape, *Histol. Histopathol.*, https://doi.org/10.14670/HH-25-116.
182. Argenziano, M. G., et al. (2026) Emerging roles of ferroptosis in modulating the immune landscape of glial tumours, *Nat. Cell Biol.*, **28**, 1364-1378, https://doi.org/10.1038/s41556-026-01972-2.
183. Zhou, Q., et al. (2024) Ferroptosis: mechanisms and therapeutic targets, *MedComm*, **5**, e70010, https://doi.org/10.1002/mco2.70010.
184. Feng, S., et al. (2023) The mechanism of ferroptosis and its related diseases, *Mol. Biomed.*, **4**, 33, https://doi.org/10.1186/s43556-023-00142-2.
185. Tang, D., et al. (2020) Ferroptosis, *Curr. Biol.*, **30**, R1292-R1297, https://doi.org/10.1016/j.cub.2020.09.068.

186. Cui, Y., et al. (2026) ACSL4 as a potential ferroptosis target in hepatocellular carcinoma: from mechanisms to implications, *Eur. J. Med. Res.*, **31**, 406, https://doi.org/10.1186/s40001-026-03993-x.
187. Fei, Y., et al. (2026) Research progress of ferroptosis in cerebral infarction, *Brain Behav.*, **16**, e71192, https://doi.org/10.1002/brb3.71192.
188. Doll, S., et al. (2019) FSP1 is a glutathione-independent ferroptosis suppressor, *Nature*, **575**, 693-698, https://doi.org/10.1038/s41586-019-1707-0.
189. Kraft, V. A. N., et al. (2020) GTP cyclohydrolase 1/tetrahydrobiopterin counteract ferroptosis through lipid remodeling, *ACS Cent. Sci.*, **6**, 41-53, https://doi.org/10.1021/acscentsci.9b01063.
190. Repges, E., et al. (2026) VKORC1L1-mediated vitamin K recycling counters ferroptosis to promote endothelial repair, *Sci. Rep.*, **16**, 19171, https://doi.org/10.1038/s41598-026-54463-7.
191. Yuan, Z., et al. (2024) Targeting NQO1 induces ferroptosis and triggers anti-tumor immunity in immunotherapy-resistant KEAP1-deficient cancers, *Drug Resist. Updat.*, **77**, 101160, https://doi.org/10.1016/j.drup.2024.101160.
192. Lin, Q., et al. (2025) Comprehensive analysis of SQOR involvement in ferroptosis resistance of pancreatic ductal adenocarcinoma in hypoxic environments, *Front. Immunol.*, **16**, 1513589, https://doi.org/10.3389/fimmu.2025.1513589.
193. Andreani, C., et al. (2025) Thioredoxin reductase 1 inhibition triggers ferroptosis in KRAS-independent lung cancers, *bioRxiv*, https://doi.org/10.1101/2025.07.25.666783.
194. Gajic, N., et al. (2025) NADPH controls a cell state vulnerability towards ferroptosis in acute lymphoblastic leukaemia, *Blood*, **146**, 144, https://doi.org/10.1182/blood-2025-144.
195. de Souza, I., et al. (2026) Tipping the balance: NRF2's dual role in ferroptotic fate, *Oncogenesis*, **15**, 26, https://doi.org/10.1038/s41389-026-00630-4.
196. Lee, J., et al. (2023) Targeting Nrf2 for ferroptosis-based therapy: implications for overcoming ferroptosis evasion and therapy resistance in cancer, *Biochim. Biophys. Acta Mol. Basis Dis.*, **1869**, 166788, https://doi.org/10.1016/j.bbadis.2023.166788.
197. Zhu, Y., et al. (2026) The dual role of ferroptosis in cancer: molecular mechanisms, microenvironment crosstalk, and precision therapeutics, *Cancers (Basel)*, **18**, 1832, https://doi.org/10.3390/cancers18111832.
198. Calabrese, C., et al. (2026) Ferroptosis as a therapeutic vulnerability to overcome chemoresistance in gastric cancer, *Pharmaceuticals (Basel)*, **19**, 949, https://doi.org/10.3390/ph19060949.
199. Kim, R., et al. (2022) Ferroptosis of tumour neutrophils causes immune suppression in cancer, *Nature*, **612**, 338-346, https://doi.org/10.1038/s41586-022-05443-0.
200. Wahida, A., et al. (2025) Decoding ferroptosis for cancer therapy, *Nat. Rev. Cancer*, **25**, 910-924, https://doi.org/10.1038/s41568-025-00864-1.
201. Mishima, E., et al. (2025) Recommendations for robust and reproducible research on ferroptosis, *Nat. Rev. Mol. Cell Biol.*, **26**, 615-630, https://doi.org/10.1038/s41580-025-00843-2.
202. Tonnus, W., et al. (2021) Dysfunction of the key ferroptosis-surveilling systems hypersensitizes mice to tubular necrosis during acute kidney injury, *Nat. Commun.*, **12**, 4402, https://doi.org/10.1038/s41467-021-24712-6.
203. Palma, M., et al. (2026) Lymph node environment drives FSP1 targetability in metastasizing melanoma, *Nature*, **649**, 477-486, https://doi.org/10.1038/s41586-025-09709-1.
204. Hendricks, J. M., et al. (2023) Identification of structurally diverse FSP1 inhibitors that sensitize cancer cells to ferroptosis, *Cell Chem. Biol.*, **30**, 1090-1103.e7, https://doi.org/10.1016/j.chembiol.2023.04.007.
205. Hangauer, M. J., et al. (2017) Drug-tolerant persister cancer cells are vulnerable to GPX4 inhibition, *Nature*, **551**, 247-250, https://doi.org/10.1038/nature24297.
206. Viswanathan, V. S., et al. (2017) Dependency of a therapy-resistant state of cancer cells on a lipid peroxidase pathway, *Nature*, **547**, 453-457, https://doi.org/10.1038/nature23007.
207. Lu, Z., et al. (2023) The potential of ferroptosis combined with radiotherapy in cancer treatment, *Front. Oncol.*, **13**, 1085581, https://doi.org/10.3389/fonc.2023.1085581.
208. Ubellacker, J. M., et al. (2020) Lymph protects metastasizing melanoma cells from ferroptosis, *Nature*, **585**, 113-118, https://doi.org/10.1038/s41586-020-2623-z.
209. Conrad, M., et al. (2020) A cozy niche in an iron world, *Signal Transduct. Target. Ther.*, **5**, 261, https://doi.org/10.1038/s41392-020-00368-4.
210. Guo, R., et al. (2023) Depriving tumor cells of ways to metastasize: ferroptosis nanotherapy blocks both hematogenous metastasis and lymphatic metastasis, *Nano Lett.*, **23**, 3401-3411, https://doi.org/10.1021/acs.nanolett.3c00365.
211. Xu, Y., et al. (2025) Ferroptosis: a novel perspective on tumor immunotherapy, *Front. Immunol.*, **16**, 1524711, https://doi.org/10.3389/fimmu.2025.1524711.
212. Wang, Z., et al. (2026) Ferroptosis induction enhances anti-PD-1 efficacy in NSCLC via HIF-1α/PD-L1 modulation, *Transl. Oncol.*, **65**, 102685, https://doi.org/10.1016/j.tranon.2026.102685.

213. Gan, L., et al. (2025) Ferroptosis meets cancer immunotherapy: overcoming the crosstalk challenges through advanced drug delivery strategies, *Acta Pharm. Sin. B*, **15**, 6307-6341, https://doi.org/10.1016/j.apsb.2025.09.043.
214. Ruiz, C. F., et al. (2026) Diet-induced phospholipid remodeling dictates ferroptosis sensitivity and tumorigenesis in the pancreas, *Cancer Discov.*, **16**, 2108-2129, https://doi.org/10.1158/2159-8290.CD-25-0734.
215. Luo, J., et al. (2025) Low dose radiotherapy combined with immune checkpoint inhibitors induces ferroptosis in lung cancer via the Nrf2/HO-1/GPX4 axis, *Front. Immunol.*, **16**, 1558814, https://doi.org/10.3389/fimmu.2025.1558814.
216. Yeerkenbieke, G., et al. (2026) Dual targeting of chemoresistance and ferroptosis in gastric cancer: DDR1/VEGFR2 inhibitor K-13 synergizes with docetaxel from preclinical models to phase Ib/II clinical trial, *Cell Death Differ.*, https://doi.org/10.1038/s41418-026-01751-4.
217. Hanahan, D. (2026) Hallmarks of cancer—then and now, and beyond, *Cell*, **189**, 2254-2277, https://doi.org/10.1016/j.cell.2025.12.049.
218. Hanahan, D., et al. (2000) The hallmarks of cancer, *Cell*, **100**, 57-70, https://doi.org/10.1016/s0092-8674(00)81683-9.
219. Eskander, G., et al. (2025) Insights on the crosstalk among different cell death mechanisms, *Cell Death Discov.*, **11**, 56, https://doi.org/10.1038/s41420-025-02328-9.
220. Shen, S., et al. (2023) Different types of cell death and their shift in shaping disease, *Cell Death Discov.*, **9**, 284, https://doi.org/10.1038/s41420-023-01581-0.
221. Ploumaki, I., et al. (2023) Bcl-2 pathway inhibition in solid tumors: a review of clinical trials, *Clin. Transl. Oncol.*, **25**, 1554-1578, https://doi.org/10.1007/s12094-022-03070-9.
222. Hodgson, S. V., et al. (2025) Inherited susceptibility to cancer: past, present and future, *Ann. Hum. Genet.*, **89**, 354-365, https://doi.org/10.1111/ahg.70013.
223. Imyanitov, E. N., et al. (2023) Hereditary cancer syndromes, *World J. Clin. Oncol.*, **14**, 40-68, https://doi.org/10.5306/wjco.v14.i2.40.
224. Imyanitov, E., et al. (2005) Polymorphic variations in apoptotic genes and cancer predisposition, *Cell Death Differ.*, **12**, 1004-1007, https://doi.org/10.1038/sj.cdd.4401674.
225. Vince, J. E., et al. (2026) The PANoptosis hypothesis examined, *Nat. Rev. Mol. Cell Biol.*, **27**, 559-560, https://doi.org/10.1038/s41580-026-00970-4.
226. Tweedell, R. E., et al. (2026) Single-cell evidence for PANoptosome complexes, *Nat. Rev. Mol. Cell Biol.*, **27**, 634-635, https://doi.org/10.1038/s41580-026-00994-w.
227. Rodrigues de Souza, E., et al. (2025) Integrated multi-optosis model for pan-cancer candidate biomarker and therapy target discovery, *Front. Bioinform.*, **5**, 1630518, https://doi.org/10.3389/fbinf.2025.1630518.
228. Fernández-Acosta, R., et al. (2025) Harnessing ferroptosis for precision oncology: challenges and prospects, *BMC Biol.*, **23**, 57, https://doi.org/10.1186/s12915-025-02154-6.
229. Moiseenko, F., et al. (2026) Surgical removal of residual tumor masses in patients undergoing targeted therapy for EGFR-mutated locally advanced or metastatic lung cancer, *Int. J. Cancer*, **159**, 2244-2261, https://doi.org/10.1002/ijc.70543.
230. Wang, Z., et al. (2025) Drug-tolerant persister cells in cancer: bridging the gaps between bench and bedside, *Nat. Commun.*, **16**, 10048, https://doi.org/10.1038/s41467-025-66376-6.
231. Lopez-Gonzalez, J. S., et al. (2026) Drug-tolerant persister cells in cancer: a scoping review of definitions, models, and molecular mechanisms, *Front. Oncol.*, **16**, 1771061, https://doi.org/10.3389/fonc.2026.1771061.
232. Maass, P., et al. (2026) Venetoclax and hypomethylating agents synergize to increase cell death and metabolic remodeling in acute B-lymphoblastic leukemia cells, *Mol. Metab.*, **110**, 102402, https://doi.org/10.1016/j.molmet.2026.102402.
233. Lopez, A., et al. (2022) Co-targeting of BAX and BCL-XL proteins broadly overcomes resistance to apoptosis in cancer, *Nat. Commun.*, **13**, 1199, https://doi.org/10.1038/s41467-022-28741-7.
234. Valentini, E., et al. (2023) Bcl-2 family inhibitors sensitize human cancer models to therapy, *Cell Death Dis.*, **14**, 441, https://doi.org/10.1038/s41419-023-05963-1.
235. Noreen, S., et al. (2025) Recent insights and applications of nanocarriers-based drug delivery systems for colonic drug delivery and cancer therapy: an updated review, *Crit. Rev. Oncol. Hematol.*, **208**, 104646, https://doi.org/10.1016/j.critrevonc.2025.104646.

Publisher's Note. Pleiades Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations. AI tools may have been used in the translation or editing of this article.