BIOLOGICA NYSSANA
16 (2) December 2025:
DOI: 10.46793/BiolNyss.16.2.8L

Cell deaths and their associated mechanisms

Original Article

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Abstract:
Cell death is a crucial process in every organism, maintaining a balance between the number of new cells generated through mitosis and the number of damaged or unnecessary cells removed from the body. It happens from the embryonic process throughout every life stage of a human being. Regulated cell death, known as apoptosis, is the most common form, while accidental or uncontrolled cell death, known as necrosis, is associated with pathological processes. In addition to these types of cell death, there are numerous other types, including necroptosis (a controlled cell death with an inflammatory process) and autophagy (mainly a part of the immune process). It is important to note that inhibition of regulated cell death can impact the normal cell cycle and can lead to drug resistance. A classic example of dysfunctional cell death regulation is cancer development. This review summarizes cell death types and their associated mechanisms.

Key words:
accidental cell death, apoptosis, necrosis, regulated cell death

Apstrakt:
Ćelijske smrti mehanizmi udruženi sa njima
Ćelijska smrt je ključni proces u svakom organizmu, jer održava ravnotežu između broja novih ćelija nastalih mitozom i broja oštećenih ili nepotrebnih ćelija uklonjenih iz organizma. Ona se odvija od embrionalnog razvoja pa tokom svih životnih stadijuma čoveka. Regulisana ćelijska smrt, poznata kao apoptoza, predstavlja najčešći oblik, dok je slučajna ili nekontrolisana ćelijska smrt, poznata kao nekroza, povezana sa patološkim procesima. Pored ovih oblika ćelijske smrti, postoji i niz drugih tipova, uključujući nekroptozu (regulisanu ćelijsku smrt sa inflamatornim procesom) i autofagiju (uglavnom deo imunskog procesa). Važno je napomenuti da inhibicija regulisane ćelijske smrti može uticati na normalan ćelijski ciklus i dovesti do rezistencije na lekove. Klasičan primer disfunkcionalne regulacije ćelijske smrti jeste razvoj kancera. Ovaj pregled sumira tipove ćelijske smrti i njihove povezane mehanizme.

Ključne reči:
slučajna ćelijska smrt, apoptoza, nekroza, regulisana ćelijska smrt

Received: June 29, 2025
Revised: September 04, 2025
Accepted: September 04, 2025

Introduction

Every organism, either multicellular and unicellular, has a specific mechanism to preserve a homeostatic state between the amount of new cells that emerged through mitosis and the number of damaged or unfavorable cells that need to be eliminated from the organism's body (Spiesser et al., 2012; Alvarado et al., 2018). Continuous cell turnover is essential to produce physical features that consist of fingers and toes, which emerge after developing from the webbed limbs first noticed in the human fetus, observed around week 10 of gestation (Hurle & Ganan, 1986). Meanwhile, uncontrolled cellular proliferation and growth may cause the development of several debilitating diseases, with cancer as the main example (Feitelson et al., 2015). In contrast, an extremely high cell death rate can lead to many disorders, including rheumatoid arthritis, Alzheimer's disease (AD), and Parkinson's disease (Gorman, 2008; D'Arcy, 2019).

Cell death can occur through several mechanisms. It can happen in a programmed (controlled) way, encompassing a multitude of biochemical, physical, and molecular operations, as well as uncontrolled ones, resulting in the leakage of cell contents into neighboring tissues. These processes may trigger further inflammatory response (particularly in unprogrammed cell death) or not (Fink & Cookson, 2005). Apoptosis, a type of regulated cell death, is considered as the most prevalent type of cell death with its importance

throughout the body (D'Arcy, 2019). Meanwhile, the uncontrolled or accidental form of cell death is called necrosis, which is particularly associated with pathological processes (including hypoxia, microbial infection, physical stress, and chemical agents) (Fathima et al., 2023) .

The mechanisms associated with mitosis regulation (stimulation or inhibition), cellular abnormality detection, and programmed cell death (PCD) initiation (apoptosis, pyroptosis or autophagy) in animals involve a long list of regulatory genes (D'Arcy, 2019). While the cell cycle and cell death require a complicated interaction of gene products, certain receptors, enzymes, and regulatory proteins have been discovered to play key roles in those events. Mutations or aberrant expression of these regulatory proteins may affect the normal cell cycle (Whitfield et al., 2002; Abreu Velez & Howard, 2015). For example, enzymes of the B-cell lymphoma-2 (BCL-2) family and transglutaminase-2 either trigger or inhibit apoptosis based on their expression (upregulation or downregulation), localization or conformation (Budillon et al., 2013; Murphy et al., 2013). Regulated cell death inhibition may directly affect cancer cells' susceptibility to chemotherapeutic drugs, resulting in drug resistance (Mansoori et al., 2017). This is illustrated in the case of increased transglutaminase-2 expression, which is associated with poor prognosis and relapse of acute myelocytic leukemia (AML) (Pierce et al., 2013; Jacamo et al., 2016). This review will briefly overview cell death types and their associated mechanisms.

Cell death: classification and explanation

The classification of cell death was initially based on the morphology and structure of tissues and cells. One of the earliest classifications was made by Schweichel and Merker in 1973, when they published a system based on morphology to classify three types of cell death, namely type I, type II, and type III (Schweichel & Merker, 1973). Type I cell death, also known as apoptosis, is defined by cellular shrinkage (pyknosis), membrane prominence (blebbing), apoptotic body emergence, deoxyribonucleic acid (DNA) disintegration (karyorrhexis), and chromatin condensation (Portt et al., 2011). This type of cell death is additionally recognized as shrinkage necrosis, considered a type of non-pathologic cell death first described by a team of investigators led by John Kerr (1971). Next, Type II cell death is defined as autophagy-dependent cell death that results in the formation of autophagic vacuoles consisting of cytoplasmic substances and organelles to create autophagic bodies. The process is mediated through lysosomal involvement and may be observed in several cases, broadly classified as micro- and macroautophagy (Todde et al., 2009; Denton & Kumar, 2019). Meanwhile, type III cell death, frequently designated as necrosis, is marked by membrane damage and expansion of subcellular organelles. Necrosis is widely defined as uncontrollable cell death and is mainly a pathological process (Tang et al., 2019).

For several decades, apoptosis was regarded as the only plausible kind of programmed cell death (Suzanne & Steller, 2013). Necrosis, conversely, was perceived as an unregulated, inadvertent consequence of excessive physical or chemical injury. However, this dichotomy has been superseded by a more nuanced, function-oriented framework determined by the Nomenclature Committee on Cell Death (NCCD) (Galluzzi et al., 2018). Currently, cell death has been classified as either accidental cell death (ACD) or regulated cell death (RCD), depending on functionality. ACD is prompted by a sudden assault or damage that disables all conceivable control systems. RCD, on the other hand, has a distinct signaling cascade carried out by a specialized set of effector molecules, as well as distinctive activities, molecular structures, and immunological consequences. It can also be pharmacologically or genetically modulated (Galluzzi et al., 2018; Van der Meeren et al., 2023). RCD is referred to as PCD when it develops under physiological conditions, such as during embryonic development (Díaz-Mendoza et al., 2013; Tang et al., 2019). RCD can be divided into at least eleven types depending on its molecular features, including apoptosis, necroptosis, pyroptosis, ferroptosis, entotic cell death, Netotic cell death (NETosis), parthanatos, lysosome-dependent cell death (LCD), autophagy-dependent cell death, alkaliptosis, and oxeiptosis (Galluzzi et al., 2018). This paradigm shift was prompted by the realization that necrosis, equivalent to apoptosis, can occur in a regulated fashion, a phenomenon now termed necroptosis, which serves as a host protective mechanism, exhibiting antipathogenic and anticancer properties (Khoury et al., 2020; Ye et al., 2023).

Accidental cell death: necrosis

Necrosis (**Fig. 1**), unlike apoptosis, is an unregulated type of cell death that occurs due to sudden external insults such as hypoxia, radiation, extreme heat, and toxins that cause severe damage and render cells unable to function properly. This process frequently entails a surge in the expression of diverse pro-inflammatory factors, such as nuclear factor-κB (Li et al., 2001). These scenarios result in cell swelling (oncosis) followed by rupture of the cell membrane, leading to a release of cell contents to the surrounding region, which triggers an inflammatory

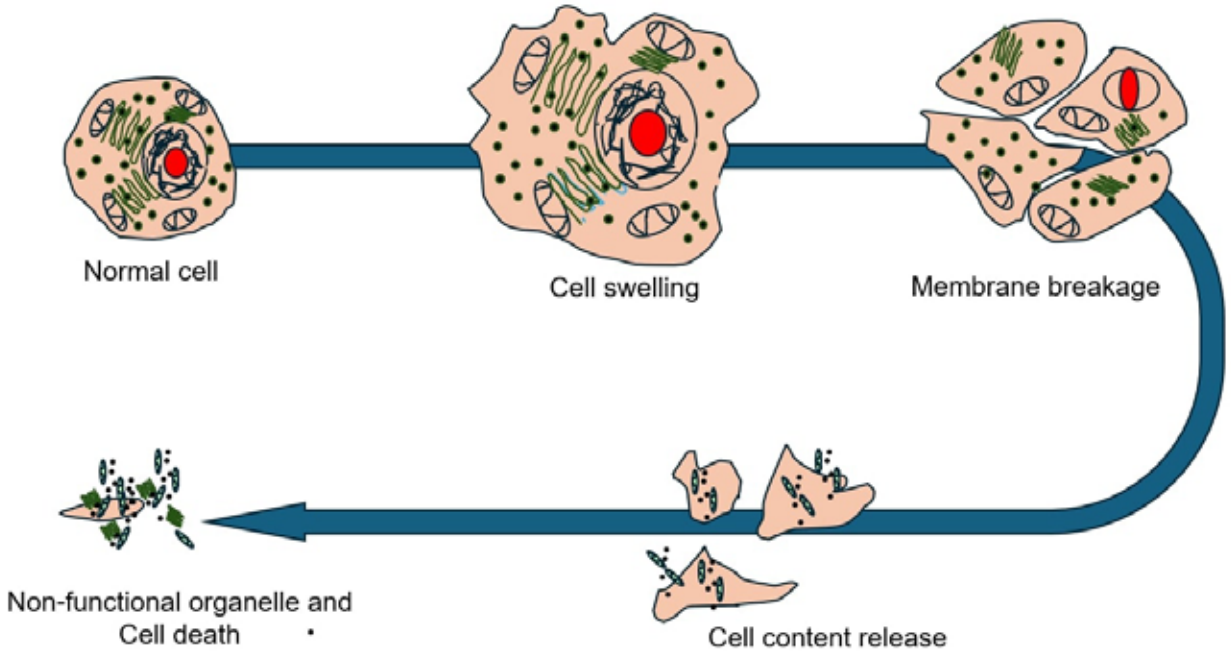

Fig. 1. Necrosis process

chain reaction and leads to tissue breakdown (Helgoe et al., 2024). Overall, the necrosis process does not require energy.

The notion of necrosis as a contrast to apoptosis is valuable. However, in cell culture, what is frequently referred to as the necrosis process is basically the remains of cells in the late-stage apoptotic events, where there is a compromised structural integrity of apoptotic bodies. This typically appears as the presence of cellular chunks in the media, which is mistakenly attributed to necrosis (Berghe et al., 2010). Within a living organism, phagocytosis typically occurs, where circulating white blood cells devour and remove these apoptotic bodies. However, in a monoculture, this phagocytosis process does not occur (Liang et al., 2014). This can complicate identifying the precise process by which cell death occurs.

Regulated cell death

Apoptosis

Apoptosis (**Fig. 2**) is considered the archetypal form of RCD, a meticulously orchestrated process of cellular self-dismantling directed by a family of cysteine-aspartic proteases known as caspases (Brentnall et al., 2013). Caspases may be classified into two groups: initiator and executor caspases. Initiator caspases (caspases 8 and 9) are activated from dormant procaspase forms upon detection of cell injury, and they subsequently trigger executor caspases (caspases 3, 6, and 7) (Aral et al., 2019). These enzymes initiate a series of processes that lead to DNA fragmentation via endonuclease activation, nuclear protein disintegration, cytoskeleton disruption, protein crosslinking, production of ligands for phagocytic cells, and apoptotic body formation. An important feature to note is that the cell membrane remains intact as the cell is packaged into smaller, membrane-bound vesicles called apoptotic bodies during the process (Zhao et al., 2021). Macrophages then swiftly phagocytose the apoptotic bodies that have formed, leading to the non-inflammatory removal of malignant and precancerous cells and a decrease in tissue damage from erroneous immune reactions (Hirayama et al., 2017).

Apoptosis is estimated to occur at a rate of 1×10^9 cells daily in the human body (Elliott & Ravichandran, 2010). This process is characterized by an interruption of cell division and expansion, followed by a sequence of steps to prepare the cell for controlled death so that its materials do not leak into the vicinity (D'Arcy, 2019).

Apoptosis may occur through two major pathways (Nosalova et al., 2023): The intrinsic (mitochondrial) pathway, responsive to intracellular stressors such as DNA damage and regulated by the B-cell lymphoma-2 (BCL-2) protein family, and the extrinsic (death receptor/DR) pathway, initiated by extracellular ligands such as tumor necrosis factor (TNF) or Fas ligand (FasL). The complementary actions of extrinsic and intrinsic apoptotic pathways guarantee that damaged cells are eliminated from the body and multicellular organisms continue to function normally (Zhong et al., 2020; Nosalova

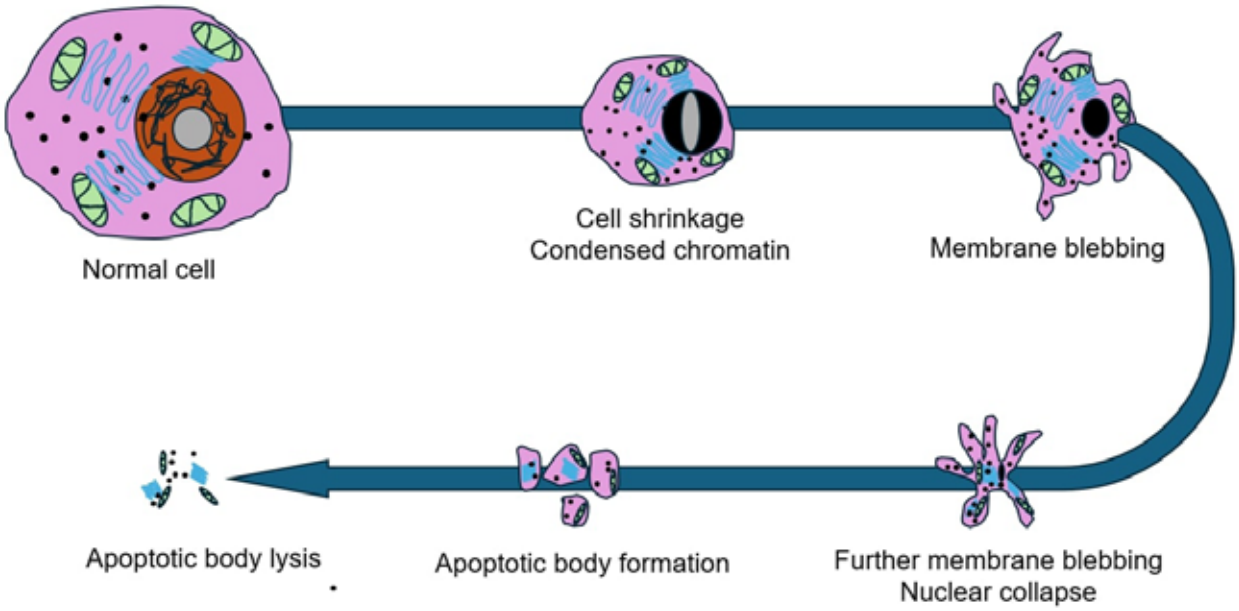

Fig. 2. Apoptosis process

et al., 2023). Apoptosis regulation issues can result in pathological conditions in several diseases. For instance, in degenerative illnesses like AD, where caspase overactivation—a crucial class of enzymes implicated as an apoptosis driver—appears to be the cause of neuronal death (Sheffield et al., 2006). This is also a necessary process to prevent malignancy (Abastado, 2015).

The intrinsic pathway of apoptosis can be initiated from a positive or negative process and depends on chemicals generated from the mitochondria. The lack of growth factors, hormones, and cytokines in the cell's surroundings produces negative signals (Orzaez et al., 2009). In addition, several cellular pro-apoptotic molecules, such as Puma, Noxa, and Bax, which are typically suppressed in a physiological state, become active and are able to start apoptosis after reaching the activation threshold and with a deficiency of the previously mentioned pro-survival signals (Zhang et al., 2016). Positive situations, including hypoxia, poisons, radiation, reactive oxygen species overproduction, viruses, and different hazardous agents, are additional variables that trigger apoptosis (Guhl et al., 2003; Sun & Mei, 2024).

Two subsets of BCL-2 proteins known as anti-apoptotic proteins, including BCL-2, Bcl-XL, BCL-W, Bfl-1, and Mcl-1, control the intrinsic pathway (Zhu et al., 2007). These substances control apoptosis by preventing the release of Cytochrome c (Cytc) from mitochondria. On the other hand, apoptosis is regulated by pro-apoptotic proteins like Hrk, Bak, Bad, Bcl-Xs, Bid, Bik, and Bim, which release Cytc from mitochondria (Liu et al., 2013). Caspases 8 and 9 are activated, and apoptosomes are formed due to the release of Cytc from mitochondria. Cell death is caused by the activation of caspase-3 by these activated caspases (Aral et al., 2019).

The extrinsic mechanism of apoptosis involves specific receptors binding to ligands, forming a DISC complex, and activating caspases. This pathway is initiated when NK cells or macrophages produce death ligands that bind to the DR on the target cell membrane (Schulze-Osthoff et al., 1998; Park et al., 2012). The role of these death receptors in the extrinsic pathway is significant, as they trigger the pathway by activating procaspase 8 to caspase 8 (Schulze-Osthoff et al., 1998).

There are several DR types, such as CD95 (also known as Fas and APO-1, Tumor Necrosis Factor/TNF Receptor 1 (TNFR1), TNF receptor superfamily member 25 (TNFRSF25)/DR3, TNF-related apoptosis-inducing ligand receptor 1 (TRAIL-R1)/DR4, and TNF-related apoptosis-inducing ligand receptor 2 (TRAIL-R2)/DR5 (Fossati et al., 2012; Bittner et al., 2016). However, the first two receptors are the most well-known ones. These receptors contain a death domain, which requires adaptor proteins to operate properly, such as the Fas-associated death domain (FADD) and TNF receptor-associated death domain (TRADD). These proteins bind to the death receptor, strengthening the ligand-receptor-adaptor protein complex known as the death-inducing signaling complex (DISC) (Fossati et al., 2012; Cavalcante et al., 2019). DISC then activates Procaspase 8, which later activates

caspase 8 and triggers apoptosis (Kober et al., 2011).

Necroptosis

In 2005, a new cell death variant was discovered which resembled necrosis but had distinct characteristics. It is an alternate form of necrosis; however, in this circumstance, cells may undergo necrosis in a controlled manner (Conrad et al., 2016), implying that apoptosis is not necessarily the favored mode of cell death. This sort of cell death is known as necroptosis (Degterev et al., 2005).

Necroptosis is a pro-inflammatory, lytic RCD type that serves as an established viral defense process that allows cells to commit „cellular suicide" in a caspase-independent fashion in the presence of viral caspase inhibitors (associated with apoptosis blockage) to limit virus reproduction (Orzalli & Kagan, 2017). Furthermore, necroptosis has been linked to inflammatory disorders occurring in several organ systems, including the pulmonary, gastrointestinal, neurological, and cardiovascular systems (Khoury et al., 2020).

In an environment-deprived scenario, necroptosis is modulated by the receptor-interacting proteins 1 and 3 (RIP1 and RIP3) (Moriwaki et al., 2015). The DR is the most recognized activation mechanism for necroptosis, which is most typically driven by TNFR1. Simultaneously, other factors, including tumor necrosis factor receptor-related apoptosis-inducing ligand (TRAIL) and the Fas receptor, may act to trigger necroptosis (Kim & Li, 2013). Ligand attachment to TNFR1 can initiate pro-survival complex I activation, including TNFR-associated death domain (TRADD), RIP1, and some E3 ubiquitin ligases. RIP1 is polyubiquitinated within the complex I; meanwhile, deubiquitination of RIP1 causes the formation of complex IIa or IIb. Complex IIa drives caspase 8 activation and induces apoptosis, while its inhibition results in the formation of complex IIb, which stimulates necroptosis (Chen et al., 2019).

To initiate necroptosis, complex IIb requires RIP1 to partner with RIP3 and cause auto- and trans-phosphorylation, which leads to the oligomerization of phosphorylated RIP3. This results in the formation of necrosomes, which are amyloid-like multiprotein complexes that distinguish them from uncontrolled necrosis. Morphologically, necroptosis mimics unregulated necrosis, marked by oncosis, the eventual burst of the plasma membrane, and the release of pro-inflammatory intracellular components. Mixed lineage kinase domain-like pseudokinase (MLKL), in addition to RIP1 and RIP3, has a role in necroptosis (Cho et al., 2009; Berghe et al., 2014). RIP3 recruits MLKL and phosphorylates it at Threonine 357 and Serine 358. Following phosphorylation, MLKL oligomerizes and shifts from the cytoplasm to the cell membrane. This causes membrane permeabilization, probably owing to MLKL attachment to phosphatidylinositol lipids and cardiolipin, which results in cell death (Loftus et al., 2022).

Ferroptosis

Ferroptosis is a unique type of RCD defined by the accumulation of lipid peroxides to fatal amounts based on an iron-dependent process (Miao et al., 2023). It is distinguished biochemically and structurally from other forms of cell death and is typified by compression of the mitochondria and greater cellular membrane density with sparing of the nucleus. Ferroptosis is caused when the action of pro-ferroptotic agents (such as iron and polyunsaturated fatty acids [PUFAs]) and anti-ferroptotic protection mechanisms are unmatched. Glutathione Peroxidase 4 (GPX4) is the key enzyme governing protection against ferroptosis. It utilizes glutathione (GSH) to prevent the accumulation of lipid peroxides, thereby interfering with the system Xc^- or incapacitating GPX4, which leads to unregulated lipoperoxidation and cell death (Stockwell et al., 2020). It is reliant substantially on the availability of labile iron that participates in Fenton reactions to generate reactive oxygen species (ROS) causing lipoperoxidation (Xu et al., 2024).

Pyroptosis

Classical apoptosis can be recognized by the partitioning of internal materials inside the cell and the removal of cellular debris without causing collateral injury to adjacent tissues (Fink & Cookson, 2005). Zychlinsky et al. (1992) discovered pyroptosis for the first time, a type of cell death caused by proinflammatory impulses and linked to an inflammatory process. Pyroptosis was first detected as a suicide mechanism of the Gram-negative bacterial pathogen *Shigella flexneri*-infected macrophages, and later in *Salmonella*-infected cells (Zychlinsky et al., 1992; Hilbi et al., 1998; Hersh et al., 1999). This is a highly inflammatory form of RCD mediated by the gasdermin family of pore-forming proteins, considered as a key component of the innate immune response to pathogen infection and other danger signals (He et al., 2015).

Pyroptosis is primarily instigated by the activation of inflammasomes - the intracellular multimeric sensing complexes of Pathogen-Associated Molecular Patterns (PAMPs) or Damage-Associated Molecular Patterns DAMPs (Zhang et al., 2021). Activated inflammasomes (particularly the NLRP3 inflammasome) result in cleavage and activation of inflammatory caspases like caspase-1 within

the canonical pathway or caspase-4/5 (human) and caspase-11 (mouse) within the non-canonical signaling pathway (Zhang et al., 2024). Activated caspases (for example procaspase 1 to caspase 1) cleave a gasdermin family protein, mostly Gasdermin D (GSDMD), into an N-terminal pore-forming domain and a C-terminal inhibitor domain (He et al., 2015). There is also a secretion of the pro-inflammatory cytokines interleukin 1β (IL-1β) and IL-18 in their active forms, causing cell death and the release of inflammatory cytokines into the surrounding milieu. The N-terminal cleavage product oligomerizes and inserts into the cell membrane and forms small pores which permit ions to move through, resulting to a discrepancy of internal and extracellular ionic slopes (after potassium efflux); water then permeates the cell, causing cell expansion and lysis, in addition to a collapse of cell membrane integrity (Wagatsuma & Nakase, 2020).

Autophagy

Autophagy is when cellular constituents, such as macroproteins or organelles, are engulfed in the lysosome (intracellularly) to undergo enzymatic breakdown. The lysosome subsequently digests the substrate, and all elements that cannot be reconstituted to form novel cell components or organelles are further broken down and utilized as an energy source (Ballabio & Bonifacino, 2019). Autophagy may be induced by several stressors, including nutritional shortages (calorie deprivation), signals occurring during cellular differentiation and embryogenesis, and compromised organellar interfaces. Autophagy has also been implicated in adaptive and innate immune reactions, such as defense against viral infection (He et al., 2018). Following the breakdown of intracellular pathogens, the antigen is presented to the major histocompatibility complex (MHC) class II, and the nucleic acid from the pathogenic organism is then transferred to the Toll-like receptor. Although autophagy is commonly employed in recycling cellular parts, it may also cause cell demise. It has been attributed to the clearance of senescent cells from old tissues and eradication of neoplastic tumors. Disruption of autophagy may contribute to malignant development. It is also linked (particularly in older species) to the formation of protein clumps in neurons and the aftermath of neurodegenerative disorders such as AD (Barmaki et al., 2023).

Autophagy can be classified into macro-, micro-, and selective autophagy. The most well-discussed type is macroautophagy. In macroautophagy, double-membrane vesicles known as autophagosomes envelop the whole cell surface. These autophagosomes subsequently merge with lysosomes to form autophagolysosomes, where the proteases eliminate their contents (Kroemer & Levine, 2008). Microautophagy occurs when organelles or cytosolic areas engage immediately with lysosomes. Microautophagy is considerably more targeted compared to macroautophagy and can be initiated by signaling compounds present on the outer layers of defective organelles, such as peroxisomes and mitochondria, causing lysosomes to fuse with these organelles (Settembre et al., 2013). Selective autophagy, also referred to as chaperone-mediated autophagy, occurs when a cytosolic chaperone targets proteins in the cytoplasm for union with lysosomes via communications between the chaperone and pentapeptides found in the substrate's amino acid sequence (Choi et al., 2023). The substrate protein attaches to the lysosomal receptor LAMP-2A and is transported to the lysosome for breakdown (Bandyopadhyay et al., 2008).

The autophagy process starts with the action of the ULK1 complex. A phosphoinositide-kinase (P13K) complex is needed to produce a phagophore, mainly the class III complex. PI3K itself can be classified into four classes (class IA, IB, II, and III) with two main subunit types: a regulatory and a catalytic subunit. Class IA, the most studied type of PI3K complex, has five subunits (p50α, p55α, p55γ, p85β, and p85α). Meanwhile, the one specific for the autophagy process has Vps15 as the regulatory and Vps34 as the catalytic subunit to trigger the conversion of phosphatidylinositol (PI) to phosphatidylinositol 3-phosphate (PI(3)P) (Engelman et al., 2006). The ATG16L, ATG5, and ATG12 complexes, together with the lipidated microtubule-associated protein light chain 3 (LC3II), facilitate phagophore elongation and serve as prerequisites for autophagosome construction (Park et al., 2016; Li et al., 2020). The p60 protein interacts with other proteins and is annihilated. P60 interacts with LC3II, resulting in the formation of autophagosomes that engulf target proteins and organelles. Autophagosomes then combine with lysosomes, whose contents are digested (Dice, 2007). Comparison of different major RCD types is available in **Tab. 1**.

Other RCD classifications

In addition to the previously described RCD types, several other kinds will be discussed below. This includes parthanatos, entosis, neutrophil extracellular traps (NET)osis – suicidal pathway, lysosome-dependent cell death (LCD), alkaliptosis, oxeiptosis, and anoikis (Galluzzi et al., 2018; Khan et al., 2022).

Parthanatos is an RCD that depends on poly(ADP-ribose) polymerase 1 (PARP1) (Conrad et al., 2016).

Table 1. Comparison of major regulated cell death pathways

Feature	Apoptosis	Necroptosis	Ferroptosis	Autophagy	Pyroptosis
Key Mediators	Caspases (Initiator: 8, 9; Executioner: 3, 6, 7), BCL-2 family, APAF-1	RIPK1, RIPK3, MLKL	Iron, ACSL4, GPX4, PUFAs	Atg proteins: Atg5, Atg7, Atg12, and Atg8	Gasdermins (GSDMD, GSDME), Caspases (1, 4, 5, 11), Inflammasomes
Morphology	Cell shrinkage, chromatin condensation, membrane blebbing, apoptotic bodies	Cell swelling (oncosis), membrane rupture, organelle swelling	Mitochondrial shrinkage, increased membrane density, intact nucleus	Formation of a double-membrane vesicle (autophagosome)	Cell swelling, membrane rupture, pore formation, „pyroptotic bodies"
Primary Triggers	DNA damage, growth factor withdrawal, death receptor ligation (TNF, FasL)	Death receptor ligation+caspase inhibition, PAMPs/ DAMPs, viral infection	Glutamate, GPX4 inhibition, iron overload, oxidative stress	Cellular starvation, nutrient and growth factor deprivation, cellular stress and organelle damage	PAMPs/DAMPs (e.g., LPS), pathogen infection, chemotherapy
Immunological Consequence	Generally non-inflammatory („silent")	Highly inflammatory (DAMP release)	Context-dependent, can be immunogenic	Context-dependent	Highly inflammatory (IL-1β/IL-18 release)
Key Pharmacological Modulators	**Inducers:** BH3 mimetics (e.g., Venetoclax). **Inhibitors:** Pan-caspase inhibitors (e.g., z-VAD-fmk)	**Inhibitors:** RIPK1 inhibitors (e.g., Necrostatin-1, GSK2982772), MLKL inhibitors (e.g., Necrosulfonamide)	**Inducers:** Erastin, RSL3. **Inhibitors:** Ferrostatin-1, Liproxstatin-1, Iron chelators	**Inducers:** mTOR inhibitor Rapamycin and its derivatives. **Inhibitors:** Chloroquine and Hydroxychloroquine	**Inhibitors:** Caspase-1 inhibitors (e.g., VX-765), GSDMD inhibitors

ACSL4: Acyl-CoA Synthetase Long Chain Family Member 4, **APAF-1**: Apoptotic Peptidase Activating Factor 1**, Atg**: Autophagy-related proteins, **BCL-2**: B-cell lymphoma 2, **DAMPs**: Damage-Associated Molecular Patterns, **DNA**: Deoxyribonucleic Acid, **FasL**: Fas Ligand, **GPX4**: Glutathione Peroxidase 4, **GSDMD**: Gasdermin D, **GSDME**: Gasdermin E, IL-1β: Interleukin-1 beta, IL-18: Interleukin-18, **LPS**: Lipopolysaccharide, **MLKL**: Mixed Lineage Kinase Domain-Like Pseudokinase, **mTOR**: Mammalian Target of Rapamycin, **PAMPs**: Pathogen-Associated Molecular Patterns, **PUFAs**: Polyunsaturated Fatty Acids, **RIPK1**: Receptor-Interacting Serine/Threonine-Protein Kinase 1, **RIPK3**: Receptor-Interacting Serine/Threonine-Protein Kinase 3**, RSL3**: RAS-Selective Lethal 3, **TNF**: Tumor Necrosis Factor

The process is triggered by oxidative stress, resulting in DNA injury and chromatinolysis. Parthanotic cell death does not involve the generation of apoptotic bodies or the breakdown of DNA. Furthermore, there is no cell swelling, although there is a rupture of the plasma membrane (Andrabi et al., 2008). PARP1 is a chromatin-associated nuclear protein essential for single- and double-strand DNA repair. PARP1 detects DNA damage and uses nicotinamide adenine dinucleotide (NAD+) and ATP to initiate poly(ADP-ribose)-ylation (Vekariya et al., 2024). The parthanatos cycle necessitates the involvement of the apoptotic DNase endonuclease G (ENDOG) and the apoptosis-inducing factor mitochondria-associated 1 (AIFM1, commonly referred to as AIF). The binding of PARP1 to AIFM1 induces the translocation of AIFM1 through the mitochondria to the cell nucleus, leading to parthanatotic chromatinolysis. The pathway can be obstructed by reducing PARP1 expression through the action of the poly(ADP-ribose)-degrading protein ADP-ribosylhydrolase-like 2 (ADPRHL2, often referred to as ARH3) (Wang et al., 2011; Fernández-Lázaro et al., 2024). Recently, it was discovered that macrophage migration inhibitory factor (MIF) is an AIFM1-binding protein with nuclease activity that produces large DNA fragments during parthanatos induction (Weiß et al., 2023).

Entosis is a form of cellular cannibalism wherein one cell swallows and annihilates another. Entosis and entotic cell death mostly transpire in epithelial tumor cells under several situations, including abnormal proliferation, glucose deficiency, matrix-induced mortality, and mitotic pressure (Durgan et al., 2017). Entosis is demonstrated by the appearance of cell-in-cell structures in cancer patients' urine and ascitic fluid, with a frequency proportionate to tumor stage. Cell adhesion and cytoskeletal rearrangement pathways are crucial in controlling entosis induction, even if the underlying mechanisms are unclear. Entotic cell death entails the digestion of ingested cells by host cells, involving LC3-associated phagocytosis (LAP) and the cathepsin B-mediated lysosomal degradation cascade (Martins et al., 2017). Entosis, however, does not include effector caspases and unregulated by BCL2 family proteins, important apoptotic characteristics (Li et al., 2015).

Netotic cell death (NETosis) is a form of RCD characterized by the expulsion of neutrophil extracellular traps (NETs) (Liana et al., 2022a). NETs are protein structures resembling DNA generated by cells reacting to viral or non-infectious stimuli. Elevated NETosis not only inhibits the advancement of pathogenic infiltration by sequestering harmful organisms but also induces the release of DAMPs. This process may result in autoimmune disorders (Liana et al., 2022b). NETosis is a dynamic process that responds to several stimuli, including ROS production by NADPH oxidase, autophagy, and the secretion and transference of granule enzymes such as elastase, matrix metalloproteinase (MMP), and myeloperoxidase. Subsequently, histone citrullination occurs, characterized by chromatin decondensation, cellular membrane disintegration, and the release of chromatin fibers (Jorch & Kubes, 2017).

LCD, frequently referred to as lysosomal cell death, is an instance of RCD caused by the ejection of hydrolytic enzymes into the cytoplasm as a consequence of lysosomal barrier perforation. This process happens when cells are exposed to lysosomotropic detergents (sphingosine or phosphatidic acid) and ROS (Fogde et al., 2022). Cathepsins, a class of lysosomal hydrolase enzymes, are essential in lysosomal degradation. Inhibition of cathepsin expression or action can avert LCD. Nonetheless, cathepsin is not the sole contributor to LCD, as lysosomes also sequester excess iron (Lin et al., 2010). This implies that lysosomal membrane permeation could contribute to the expulsion of this hazardous metal into the cytosol, thus triggering ferroptosis, which was discussed in a previous section (Min & Kwon, 2020).

Alkaliptosis is a newly identified type of RCD that initiates through intracellular alkalinization (Song et al., 2018). Disruption of the nuclear factor kappa B kinase subunit beta (IKBKB, or IKKβ)-NF;κβ pathway, which leads to the downregulation of carbonic anhydrase 9 (CA9), an enzyme critical for pH regulation, is an essential alkaliptosis mediator (Liu et al., 2019). It was determined following JTC801 administration, an opioid analgesic, which effectively eradicates cell lines of human malignancies, causing cellular demise that are not characteristic of with apoptosis, necroptosis, autophagy, or ferroptosis (Song et al., 2018).

Anoikis is a specific type of RCD that prohibits detached cells from surviving and populating in the wrong places. This is a vital process for preserving tissue homeostasis, making cells die after their detachment from the extracellular matrix (ECM) (Taddei et al., 2012). This phenomenon is especially significant for epithelial and endothelial cells, which greatly depend on interactions with the ECM for survival and appropriate function (Giannoni et al., 2008). Moreover, anoikis is essential to prevent metastasis of cancer cells. However, in some cases, cancer cells develop an anoikis resistance, which allows them to enter the metastatic cascade, such as by the involvement of the MUC1 extracellular domain. It enables cancer cells to withstand detachment, infiltrate the lymphatic or blood

systems, and eventually colonize far-off locations to develop secondary tumors (Zhao et al., 2014). Like apoptosis, anoikis is a process marked by cellular and molecular alterations, including membrane blebbing, chromatin condensation, DNA fragmentation, and caspase activation. These processes result in the methodical breakdown and elimination of the cell without causing an inflammatory reaction (Park et al., 2023).

Oxeiptosis is a form of RCD induced by oxygen radicals. It results from the activation of the KEAP-1-PGAM5-AIFM1 pathway. Ozone or H_2O_2-induced oxeiptosis does not engage apoptotic or pyroptotic caspases, necroptosis, autophagy, or ferroptosis (Holze et al., 2018). The KEAP1-NFE2L2 pathway is recognized for facilitating cytoprotective responses to oxidative stress. Active KEAP1 facilitates H_2O_2-induced oxeiptosis through a mechanism involving PGAM5, a mitochondrial serine-threonine phosphatase that dephosphorylates AIFM1 at Ser116 (Holze et al., 2018; Tang et al., 2019).

Therapeutic implications

The unraveling of the molecular processes governing RCD has reshaped medication development, shifting from broad cytotoxic drugs to personalized therapies designed to modulate certain cell death pathways. This approach could effectively eliminate malignant cells, such as cancer cells, or prevent cell death when it is inappropriate, as shown in neurodegenerative and inflammatory illnesses.

The evasion of apoptosis is a hallmark of cancer, enabling tumor cells to endure stress associated with the disease and resist therapeutic interventions (Mirzayans, 2024). A common method for this evasion is the overexpression of anti-apoptotic proteins from the BCL-2 group. This understanding led to the development of a class of medications known as „BH3 mimetics", which are small compounds designed to mimic the BH3-only pro-apoptotic proteins that naturally counteract their anti-apoptotic counterparts (Hassig et al., 2014; Fulda, 2015). A drug, Venetoclax, the inaugural BCL-2 inhibitor of its type, represents a significant advancement in this domain, particularly for treating numerous hematologic malignancies. In Chronic Lymphocytic Leukemia (CLL), particularly in individuals with the high-risk 17p deletion who often demonstrate resistance to conventional chemoimmunotherapy, Venetoclax has exhibited substantial and enduring results (Stilgenbauer et al., 2016). Similarly, in Acute Myeloid Leukemia (AML), the combination of Venetoclax with hypomethylating drugs (e.g., azacytidine and decitabine) has become a new standard of care (Ucciero et al., 2023).

Inhibiting cell death is the primary approach to treating numerous chronic inflammatory and neurodegenerative disorders. Halting necroptosis is thought to mitigate tissue damage and disease progression in this context. RIPK1, the primary kinase in the system, has been the principal focus of pharmacological development. The discovery of Necrostatin-1, a small-molecule inhibitor of RIPK1, represented the first pharmacological instrument to demonstrate the therapeutic effectiveness of necroptosis inhibition in many preclinical illness settings (Vandenabeele et al., 2013). Subsequently, more potent and specific next-generation RIPK1 inhibitors with enhanced pharmacological characteristics were developed and evaluated in clinical studies. Several drugs, including GSK2982772, SAR443060 (DNL747), and SAR443820 (DNL788), have been evaluated in Phase I and II trials for various neurodegenerative and inflammatory illnesses (Vissers et al., 2022; Hincelin-Mery et al., 2024; Gonen et al., 2025). Although these drugs demonstrated a favorable safety profile, its clinical application has been challenging due to the lack of significant medical benefit.

Inducing ferroptosis in cancer highlights a unique therapeutic paradox: the same procedure that kills cancer cells can also be inhibited to preserve neurons, highlighting its context-dependent role in disease. As a result, multiple preclinical studies have demonstrated the significant efficacy of tool compounds like erastin and RSL3 in diverse cancer types (Ghoochani et al., 2021). Meanwhile, several potent ferroptosis inhibitors, such as the radical-trapping antioxidants Ferrostatin-1 and Liproxstatin-1, have consistently shown advantageous neuroprotective effects in animal models of neurodegenerative diseases (Zilka et al., 2017). The therapeutic challenge is to develop ferroptosis inhibitors capable of traversing the blood-brain barrier, exhibiting high specificity, and possessing an extensive therapeutic window. The summary regarding cell death targeting to treat numerous diseases is available in **Fig. 3**.

Immunogenic cell death and anti-tumor immune response

Immunogenic Cell Death (ICD) has revolutionized the fields of cell death and immunology, illustrating that particular forms of RCD can convert dying tumor cells into a potent *in situ* vaccine capable of eliciting a robust and enduring anti-tumor immune response. This concept is now integral to contemporary cancer immunotherapy.

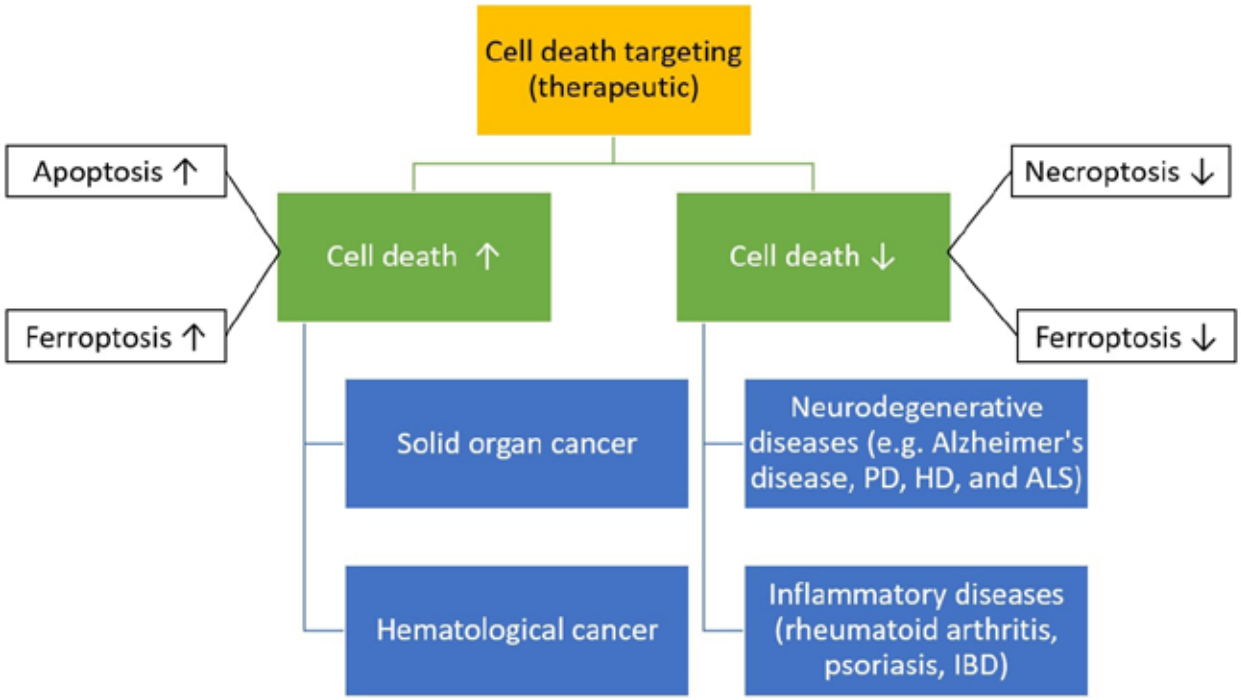

Fig. 3. Therapeutic implications of cell death regulation

An ICD is a variant of RCD that possesses sufficient strength to initiate an adaptive immune response against antigens derived from necrotic cells. The prompt release or exposure of a particular collection of molecules known as DAMPs confers this immunogenicity (Galluzzi et al., 2020). An identifiable „immunogenic triad" of DAMPs is considered the hallmark of genuine ICD. These DAMPs initiate a complex immunological response that transforms a tumor microenvironment (TME) that is unresponsive to the immune system, or „cold", into an inflamed or „hot" state, facilitating the infiltration of activated antigen-presenting cells (APCs) and effector T cells (Galluzzi et al., 2020; Solari et al., 2020; Thiruppathi et al., 2024). This mechanism initiates a tumor-specific immune cycle.

Synergistic strategies have shown improved tumor control and survival compared to singular modalities. The interaction between cell death modulators and immune checkpoint blockade (ICB) transcends drugs that induce traditional ICD within the tumor cells themselves (Arimoto et al., 2024). Research on the BCL-2 inhibitor Venetoclax in solid tumor models has revealed a significant alternative mechanism. Venetoclax, a selective BCL-2 inhibitor, eliminates naive and memory T cells reliant on BCL-2, while sparing effector T cells that depend on BCL-XL and exhibit resistance to Venetoclax. This mechanism induces an „immune-sculpting" impact in the TME, which selectively eliminates less active T-cell subsets, hence enhancing conditions for PD-1-expressing effector T cells, the primary target of immune checkpoint blockade (ICB) (Ludwig et al., 2021; Nagasaki et al., 2024).

A major challenge in the clinical application of ICD-based combination medicines is the selection of individuals who are most likely to benefit. This has prompted the quest for reliable biomarkers capable of predicting or monitoring the onset of an immunogenic response in patients. Potential biomarkers can be broadly categorized into two types: those that quantify the DAMPs directly and those that assess the ensuing immune responses (Jiang et al., 2021). Nonetheless, the results have been inconsistent across different cancer types and treatment modalities due to multiple challenges, including the technical difficulties in standardizing assays, the short half-life of these markers, and the release of DAMPs like HMGB1 during non-ICD death or sterile inflammation, which limits their specificity as ICD biomarkers (Ahmed & Tait, 2020; Thiruppathi et al., 2024).

Conclusion

Cell death is a natural process that maintains bodily homeostasis. The body's primary strategy for maintaining homeostasis is the selective elimination of dangerous or contaminated cells. This process may occur through various processes, resulting in distinct morphological alterations and immunological responses, broadly defined as controlled and uncontrolled cell death. Oxidative stress is a common cause of cell death. A greater understanding of the

many types of cell death can help design better and more effective treatments for diseases like cancer.

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