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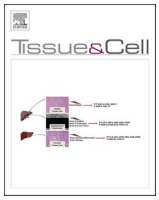

Navigating the complexities of cell death: Insights into accidental and programmed cell death

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ABSTRACT

Cell death is a critical biological phenomenon that can be categorized into accidental cell death (ACD) and programmed cell death (PCD), each exhibiting distinct signaling, mechanistic and morphological characteristics. This paper provides a comprehensive overview of seven types of ACD, including coagulative, liquefactive, caseous, fat, fibrinoid, gangrenous and secondary necrosis, discussing their pathological implications in conditions such as ischemia and inflammation. Additionally, we review eighteen forms of PCD, encompassing autophagy, apoptosis, necroptosis, pyroptosis, paraptosis, ferroptosis, anoikis, entosis, NETosis, eryptosis, parthanatos, mitoptosis, and newly recognized types such as methuosis, autosis, alkaliptosis, oxeiptosis, cuprotosis and erebosis. The implications of these cell death modalities for cellular processes, development, and disease—particularly in the context of neoplastic and neurodegenerative disorders—are also covered. Furthermore, we explore the crosstalk between various forms of PCD, emphasizing how apoptotic mechanisms can influence pathways like necroptosis and pyroptosis. Understanding this interplay is crucial for elucidating cellular responses to stress, as well as for its potential relevance in clinical applications and therapeutic strategies. Future research should focus on clarifying the molecular mechanisms that govern different forms of PCD and their interactions.

1. Introduction

Cell fate encompasses a diverse array of events that cells experience throughout their life cycle. This fascinating concept includes key processes such as proliferation, differentiation, various forms of cell death, senescence, migration, dedifferentiation, and cross-differentiation. Each of these outcomes is meticulously regulated by a complex interplay of signaling pathways and environmental interactions. Understanding the intricacies of cell fate and its underlying mechanisms is crucial for advancing treatments for a variety of significant diseases, including cancer, as well as for enhancing tissue regeneration in the field of regenerative medicine (Shen et al., 2023a; Peng et al., 2022).

Among the various aspects of cell fate, cell death has emerged as a major area of interest from both health and disease perspectives. One of the defining features of cancer cells is their failure to properly regulate the cell death, allowing tumor cells to evade death and proliferate uncontrollably. As a result, the regulation of cell death has become a focal point for some of the most promising anti-cancer treatments. By targeting the mechanisms that govern cell death, researchers aim to restore the natural balance within the body, offering new hope for effective cancer therapies and improved patient outcomes (Lockshin and Zakeri, 2007; Loftus et al., 2022). On the other hand, abnormal cell death programs, such as necroptosis and apoptosis, play a significant role in neurodegenerative diseases like Alzheimer's and Parkinson's. Understanding these pathways is crucial, as they could lead to the development of innovative treatments for these debilitating conditions. In

Abbreviations: ACD, Accidental Cell Death; AIFM1, Apoptosis-Inducing Factor Mitochondrial 1; BCL-2, B-cell lymphoma 2; CIC, Cell-In-Cell; DAMPs, Damage-Associated Molecular Patterns; DRP1, Dynamin-related protein; ECM, Extracellular Matrix; ER, Endoplasmic Reticulum; GTPases, Guanosine Triphosphate Hydrolases; GPX4, Glutathione Peroxidase 4; IL-1β, Interleukin 1 beta; IL-18, Interleukin 18; KEAP1, Kelch-Like ECH-Associated Protein 1; LACD, Planned Cell Death.; LPCD, Planned Cell Death; MLKL, Mixed Lineage Kinase Domain-Like Protein; MFF, Mitochondrial Fission Factor; PAMPs, Pathogen-Associated Molecular Patterns; PCD, Programmed Cell Death; PGAM5, Phosphoglycerate Mutase Family Member 5; PRRs, Pattern Recognition Receptors; RIPK1, Receptor-Interacting Protein Kinase 1; RIPK3, Receptor-Interacting Protein Kinase 3; ROS, Reactive Oxygen Species; SOD1, Superoxide Dismutase 1; TNF, Tumor Necrosis Factor; TNFR1, Tumor Necrosis Factor Receptor 1.

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addition to neurodegeneration, cellular dysfunction is also a hallmark of autoimmune diseases, where autoreactive cells manage to survive and perpetuate the immune response. The dynamics of cell death can significantly impact the outcome of infections as well. For instance, pyroptosis—a form of cell death associated with inflammation—can be beneficial in containing infections, but it may also lead to excessive inflammation, complicating the clinical picture (Moujalled et al., 2021; Gibellini and Moro, 2021).

Cell death can be broadly categorized into two primary types: programmed cell death (PCD) and accidental cell death (ACD). The main types of PCD are apoptosis, necroptosis, pyroptosis and autophagy (Kari et al., 2022; Chen et al., 2024). Regulated forms of cell death play essential roles in various biological processes, including embryonic development and the ongoing maintenance of tissues. These mechanisms ensure that damaged or unnecessary cells are efficiently replaced. For instance, apoptosis is crucial for tissue formation and the removal of embryonic cells in adult organisms, while autophagy facilitates the recycling of intracellular components, promoting cellular health and homeostasis. In contrast, ACD occurs as a result of a single insult or stressor, such as ischemia. Unlike the regulated processes of PCD, ACD leads to uncontrolled cell death and inflammation, which can have detrimental effects on surrounding tissues. Understanding these distinctions is vital for developing therapeutic approaches that can harness the benefits of regulated cell death while mitigating the harmful consequences of accidental cell death (Dehghan et al., 2023).

By exploring the intricate mechanisms that govern how cells determine their fates, researchers are paving the way for groundbreaking therapeutic strategies that have the potential to revolutionize patient care and enhance health outcomes. This review delved into the various types of cell death and highlights their fundamental and morphological differences (Table 1). The environmental conditions that trigger these processes and the signaling pathways involved are also explained (summarized in Table 2). This comprehensive understanding is crucial for developing targeted interventions that can effectively address a range of diseases.

2. Classification of different types of cell death

Cell death can be classified into several distinct types, each characterized by unique mechanisms and physiological implications. Broadly, cell death is categorized into PCD and ACD. In the following, the nature of these classifications will be explained, highlighting their specific characteristics and the underlying mechanisms.

2.1. Accidental cell death

Necrosis is a pathological form of cell death that occurs in living tissues and is characterized by its irreversibility and spontaneity. This process can arise from various underlying factors, including injury, infection, or ischemia. In contrast to PCD, which is an active, controlled, and well-regulated, necrosis is a passive and poorly regulated event. As a result, necrosis often leads to significant tissue damage, compromising the integrity of the affected area and triggering inflammatory responses that can further exacerbate tissue injury (Fink and Cookson, 2005; Ma. Luisa et al., 2015). Understanding the process of necrosis is crucial for identifying and managing diseases that involve tissue death, such as myocardial infarctions and infections. The progression of necrosis can be divided into several key stages that warrant further explanation. The initial stage of necrosis involves cellular injury, which can be triggered by various factors, including trauma, ischemia, and exposure to toxins. This damage primarily affects the plasma membrane, leading to an increase in its permeability. As a result, water and ions flow into the cells, causing them to swell. This swelling, known as oncosis, is a hallmark of the early stages of necrosis. As the injury persists, the cells continue to swell, and the organelles within them begin to deteriorate (Park et al., 2023). The mitochondria, in particular, are affected, leading to a decrease in ATP production and the accumulation of metabolic waste products. This metabolic disturbance further exacerbates the cellular damage. When the integrity of the membrane is severely compromised, the cell undergoes rupture, causing its internal contents to spill into the extracellular environment. This release triggers an inflammatory response, as the released molecules act as damage-associated molecular patterns (DAMPs) that alert the immune system to the presence of cellular damage (Roh and Sohn, 2018). The inflammatory response leads to the recruitment of immune cells, such as neutrophils and macrophages, which attempt to clear the damaged tissue and initiate the healing process. In addition to the cellular membrane, the cytoplasm may exhibit a granular appearance due to the breakdown of organelles, and the nucleus may undergo significant alterations, such as pyknosis (nuclear condensation), karyorrhexis (nuclear fragmentation), or karyolysis (dissolution of the nucleus). These morphological changes serve as key indicators of necrosis and help differentiate it from other forms of cell death, such as apoptosis, which is characterized by more orderly and controlled cellular dismantling (Liu et al., 2023). Main types are necrosis are as follows:

2.1.1. Coagulative necrosis

Coagulative necrosis is the most prevalent form of necrosis, typically resulting from ischemia or infarction, which compromises blood supply to affected tissues. This process is characterized by protein denaturation while maintaining the overall cellular architecture, allowing the outlines of dead cells to remain visible under microscopic examination for several days. Coagulative necrosis predominantly affects solid organs, including the heart, kidneys, and adrenal glands, but is not typically observed in brain tissue. The affected regions exhibit a firm and pale appearance due to protein coagulation, which impedes normal tissue function, but may soften over time as secondary inflammatory processes develop (Caruso et al., 2014).

2.1.2. Liquefactive necrosis

Liquefactive necrosis is a pathological process in which dead tissue is transformed into a viscous liquid mass, often resulting from bacterial infections or ischemia, particularly in the brain. This phenomenon occurs when hydrolytic enzymes released by neutrophils digest necrotic tissue, leading to the accumulation of pus. Consequently, the structural integrity of the affected tissue is compromised, resulting in a soft, creamy yellow fluid appearance. Liquefactive necrosis is often observed in conditions such as cerebral infarction, where it can be exacerbated by excitotoxicity and hypoxic cell death (Adigun R and Murray, 2024).

2.1.3. Caseous necrosis

Caseous necrosis is a distinct form of tissue death commonly associated with tuberculosis and fungal infections and sarcoidosis. This type of necrosis represents a combination of coagulative and liquefactive necrosis, where dead cells disintegrate but are not entirely digested. The affected tissue typically appears white and crumbly, resembling clumped cheese. Histologically, caseous necrosis is marked by amorphous, granular debris surrounded by a prominent inflammatory border, often leading to the formation of granulomas. These granulomas consist of aggregates of epithelioid macrophages and multinucleated giant cells, reflecting a chronic inflammatory response to infections. This process indicates an attempt by the body to contain the infection, as the immune system isolates pathogens without achieving complete clearance (Adigun R and Murray, 2024; Kandouz, 2024; Wu et al., 2023).

2.1.4. Fat necrosis

Fat necrosis is commonly associated with conditions such as pancreatitis or trauma to fat-rich regions. This type of necrosis results from the enzymatic breakdown of triglycerides by lipases, which release free fatty acids. These fatty acids can subsequently bind with calcium ions, leading to the formation of soap-like structures through a process known as saponification. Clinically, fat necrosis manifests as painful

Table 1
A comparative overview of programmed cell death mechanisms.

Type of cell death	Mechanism	Intracellular organelles involved	Key proteins involved	Morphological changes	References
Necrosis	Uncontrolled	- Plasma membrane (rupture) - Cytoplasm (swelling and leakage)	- Calpain - Caspases (in some contexts) - DAMPs	Cell swelling, membrane rupture, inflammation	(Park et al., 2023; Roh and Sohn, 2018; Karch and Molkentin, 2015)
Autophagy	Self-digestion	- Lysosomes - Endoplasmic reticulum	- LC3 (Microtubule-associated protein 1 A/1B-light chain 3) - Beclin−1 - ATG proteins (Autophagy-related proteins	Formation of autophagosome	(Yang and Klionsky, 2009; Aman et al., 2021; Parzych and Klionsky, 2014)
Apoptosis	Caspase-dependent	- Mitochondria (release of cytochrome c) - Nucleus (chromatin condensation)	- Caspases (e.g., Caspase−3, Caspase−9) - Bcl−2 family proteins (e.g., Bcl−2, Bax) - Cytochrome c - FADD	Cell shrinkage, chromatin condensation, blebbing, formation of apoptotic bodies	(Shen et al., 2023a, 2023b)
Necroptosis	Caspase-independent	- Plasma membrane (permeability changes) - Mitochondria (dysfunction)	- RIPK1 - RIPK3 - MLKL	Cell swelling, membrane rupture, release of DAMPs	(Ye et al., 2023a; Galluzzi et al., 2017; Seo et al., 2021)
Pyroptosis	Caspase-dependent	- Cytoplasm (inflammasome formation) - Plasma membrane (formation of pores)	- Caspase−1 - Caspase−4/5/11 - Gasdermin D - IL−1β - IL−18	Cell swelling, membrane rupture, release of pro-inflammatory cytokines	(Yu et al., 2021; Wei et al., 2022; Tan et al., 2021)
Paraptosis	Caspase-independent	- Endoplasmic reticulum (swelling and vacuolization) - Mitochondria (swelling)	- ER stress markers (e.g., CHOP, GRP78) - Proteasome inhibitors	Cytoplasmic vacuolation, intact nucleus, no apoptotic bodies, late mitochondrial swelling	(Kim et al., 2020; Hanson et al., 2023)
Ferroptosis	Iron-dependent	- Mitochondria (altered morphology) - Endoplasmic reticulum (lipid metabolism)	- GPX4 - Fenton reaction components (e.g., Iron) - Lipid peroxidation products	Rounded cells, reduced membrane integrity, intact nuclei	(Li et al., 2020; Hirschhorn and Stockwell, 2019; Zhang et al., 2022; Chen et al., 2021a)
Anoikis	Caspase-dependent	- Nucleus (chromatin condensation) - Plasma membrane (blebbing)	- Integrins - Caspases (e.g., Caspase−3) - Bcl−2 family proteins (pro-apoptotic members)	Cell rounding, chromatin condensation, blebbing	(Frisch, 2001; Wazir et al., 2015)
Entosis	Cell-in-cell phenomenon	- Cytoplasm (engulfed cell)- Plasma membrane (involved in engulfment)	- Caspases (in some contexts) - Actin (for engulfment process) - Rho GTPase	Formation of a 'cell-in-cell' structure	(Florey et al., 2015b; Krishna and Overholtzer, 2016; Gaptulbarova et al., 2024)
NETosis	Neutrophil activation	- Nucleus (release of chromatin) - Cytoplasm (formation of NETs)	- Caspase−1 - Neutrophil elastase - Myeloperoxidase - Histones	Release of chromatin and antimicrobial proteins into the extracellular space	(Rada, 2019; Thiam et al., 2020)
Eryptosis	Calcium-dependent	- Plasma membrane (phospholipid scrambling) - Mitochondria (influences)	- Calcium-dependent proteases- Scramblase	Membrane scrambling, cell shrinkage	(Lang et al., 2012; Pretorius et al., 2016; Alghareeb et al., 2023)
Parthanatos	PARP−1 activation	- Nucleus (DNA damage response) - Mitochondria (influences)	- PARP−1 - Caspases (in some contexts)	Chromatin condensation, nuclear fragmentation	(Liu et al., 2022; Huang et al., 2022a)
Mitoptosis	Mitochondrial fission	- Mitochondria (fission and removal)	- Drp1 (Dynamin-related protein 1) - Mff (Mitochondrial fission factor)	Mitochondrial fragmentation	(Jangamreddy and Los, 2012; Lyamzaev et al., 2020)
Methuosis	Macropinocytosis-dependent	- Endosomes - Lysosomes - Cytoplasm	- Rac1 - GIT−1 - Arf−6	Cell swelling, large vacuoles, membrane rupture	(Ye et al., 2023b; Maltese and Overmeyer, 2014; Overmeyer et al., 2011)
Autosis	Autophagy-dependent	- Lysosomes - Autophagosomes	- Beclin−1 - LC3-II - mTOR	Enlarged cytoplasm, Numerous vacuoles	(Liu and Levine, 2015; Nah et al., 2020; Yang et al., 2024)
Alkaliptosis	pH-dependent	- Mitochondria - Endoplasmic reticulum	Unknown; emerging research area	Cell swelling, membrane blebbing, organelle damage	(Chen et al., 2024; Liu et al., 2020a; Chen et al., 2023; Que et al., 2023)
Oxeiptosis	ROS-dependent	- Mitochondria - Cytoplasm	- GPX4 - P53	Enlarged cells, disrupted mitochondria, intact nucleus, no blebbing	(Park et al., 2023; Pallichankandy et al., 2023; Kang et al., 2022; Holze et al., 2018)
Cuproptosis	Copper-dependent	- Mitochondria	- FDX1 - ATP7A - SLC31A1	Cell swelling, mitochondrial dysfunction, loss of membrane integrity	(Xing et al., 2024; Xie et al., 2023; Xiong et al., 2023; Vo et al., 2024; Tang et al., 2022)
Erebosis	Metabolism-dependent	- Mitochondria - Cytoplasm	Unknown; under investigation	Cellular swelling and necrotic features	(Ciesielski et al., 2022; Bergmann, 2022)

Table 2
The role of different types of cell death in disease and health.

Type of cell death	Key characteristics	Organs involved	Role in disease	References
Necrosis	Pathological cell death due to injury or infection	- Heart (in myocardial infarction) - Brain (in ischemic stroke) - Liver (in toxin-induced injury)	Associated with tissue damage in conditions like myocardial infarction	(Fink and Cookson, 2005; Ma. Luisa et al., 2015)
Autophagy	Degradation and recycling of cellular components	- Liver (to recycle damaged organelles) - Muscle (during starvation) - Neurons (to clear protein aggregates)	Maintains cellular homeostasis; dysregulation linked to various diseases	(Shen et al., 2023a, 2023b; Parzych and Klionsky, 2014)
Apoptosis	Controlled cell death; removes damaged or unnecessary cells	- Thymus (during development) - Intestine (to maintain epithelial lining) - Ovary and Testis (to remove excess germ cells)	Implicated in cancer, autoimmune diseases, and tissue homeostasis	(Shen et al., 2023a; Ameisen, 2002)
Necroptosis	Hybrid of necrosis and apoptosis, often as a backup mechanism	- Intestine (in inflammatory bowel diseases) - Brain (in neurodegenerative disorders) - Heart (in ischemia-reperfusion injury)	Involved in inflammatory responses and tissue damage	(Fink and Cookson, 2005; Park et al., 2021; Dhuriya and Sharma, 2018)
Pyroptosis	Inflammatory cell death triggered by pathogens	- Macrophages (in response to pathogens) - Intestinal epithelial cells (in infectious diarrhea) - Neurons (in neurodegenerative diseases)	Important in host defense against infections	(Bergsbaken et al., 2009; Yu et al., 2021; Wei et al., 2022; Tan et al., 2021)
Paraptosis	Characterized by ER and mitochondrial swelling	- Various tissues (in response to stress)	Associated with cellular stress responses	(Kim et al., 2020; Hanson et al., 2023)
Ferroptosis	Cell death driven by lipid peroxidation and oxidative stress	- Kidney (in acute kidney injury) - Brain (in Parkinson's and Huntington's diseases) - Liver (in hepatocellular carcinoma)	Implicated in cancer and neurodegenerative diseases	(Yan et al., 2021; Li et al., 2020; Hirschhorn and Stockwell, 2019)
Anoikis	Cell death due to loss of attachment to the extracellular matrix	- Epithelial cells (to prevent detachment and metastasis) - Endothelial cells (to maintain vascular integrity) - Fibroblasts (to regulate wound healing)	Prevents detached cells from proliferating; relevant in cancer metastasis	(Han et al., 2023; Adeshakin et al., 2021)
Entosis	One cell engulfs another, leading to various outcomes	- Breast cancer cells (to promote tumor growth) - Colon cancer cells (to increase ploidy) - Retinal pigment epithelial cells (in age-related macular degeneration)	Observed in cancer; may contribute to tumor growth	(Florey et al., 2015a; Kim et al., 2024)
NETosis	Formation of neutrophil extracellular traps (NETs) to trap pathogens	- Neutrophils (to trap and kill pathogens) - Lungs (in acute respiratory distress syndrome) - Blood vessels (in thrombosis)	Plays a role in innate immunity and inflammation; implicated in autoimmune diseases	(Brinkmann et al., 2004; Delgado-Rizo et al., 2017)
Eryptosis	Programmed death of erythrocytes	- Erythrocytes (red blood cells)	Implicated in anemia and other erythrocyte disorders	(Lang et al., 2012; Pretorius et al., 2016; Alghareeb et al., 2023)
Parthanatos	Cell death associated with extensive DNA damage	- Nervous system (in neurodegenerative conditions)	Linked to neurodegenerative diseases and ischemic injury	(Liu et al., 2022; Huang et al., 2022a)
Mitoptosis	Removal of damaged mitochondria	- Mitochondrial-rich tissues (e.g., muscle, brain	Important in maintaining mitochondrial quality control	(Jangamreddy and Los, 2012; Lyamzaev et al., 2020)
Methuosis	Characterized by large fluid-filled vacuoles from macropinocytosis, leading to cell swelling and membrane rupture	Primarily observed in cancer cells	Implicated in tumor progression and resistance to apoptosis	(Bielsa et al., 2022; Ye et al., 2023b)
Autosis	Involves excessive autophagy leading to cell death, with extensive cytoplasmic vacuolization	Various tissues, particularly in response to stress	Associated with neurodegenerative diseases and cancer	(Bai et al., 2023; Fulda and Kögel, 2015)
Alkaliptosis	Induced by alkaline stress, causing cellular dysfunction and membrane disruption	Potentially affects multiple organs, but specific studies are limited	May contribute to conditions like metabolic alkalosis or tissue damage from alkalinity	(Liu et al., 2020a; Chen et al., 2023)
Oxeiptosis	Triggered by oxidative stress, resulting in cell death through ROS accumulation	Commonly affects tissues with high metabolic activity (e.g., brain, heart)	Linked to neurodegenerative diseases and ischemic injury	(Park et al., 2023; Pallichankandy et al., 2023; Kang et al., 2022; Holze et al., 2018)
Cuproptosis	Copper-induced cell death through mitochondrial dysfunction and proteotoxic stress, characterized by cell swelling	Primarily affects liver and kidney tissues due to copper metabolism	Associated with copper toxicity and certain liver diseases	(Xing et al., 2024; Xie et al., 2023; Xiong et al., 2023; Vo et al., 2024; Tang et al., 2022)
Erebosis	Characterized by metabolic dysregulation leading to cell death; specific mechanisms are still under investigation	Potentially widespread across various organ systems	May play a role in metabolic disorders and age-related diseases	(Ciesielski et al., 2022; Bergmann, 2022)

lumps or localized inflammation in areas such as the pancreas or breast. The necrotic adipose tissue exhibits a chalky white appearance due to these biochemical alterations (Adigun R and Murray, 2024; Wu et al., 2023).

2.1.5. *Fibrinoid necrosis*

Fibrinoid necrosis primarily occurs in small blood vessels as a result of immune-mediated vascular damage. In this process, immune complexes and fibrin-like protein deposits accumulate along the vessel walls, resulting in a distinctive eosinophilic appearance when viewed under a microscope. Additionally, deposition of fibrin lead to complications in tissue perfusion and function, potentially resulting in ischemia or necrosis of surrounding tissues. This type of necrosis is commonly associated with conditions such as vasculitis and severe hypertension, reflecting an inflammatory response that undermines vascular integrity (Fink and Cookson, 2005; Adigun R and Murray, 2024).

2.1.6. *Gangrenous necrosis*

Gangrenous necrosis refers to tissue death caused by severe ischemia, most commonly affecting extremities such as the toes and fingers. This type of necrosis can be classified into two distinct forms: dry gangrene and wet gangrene. Dry gangrene is characterized by

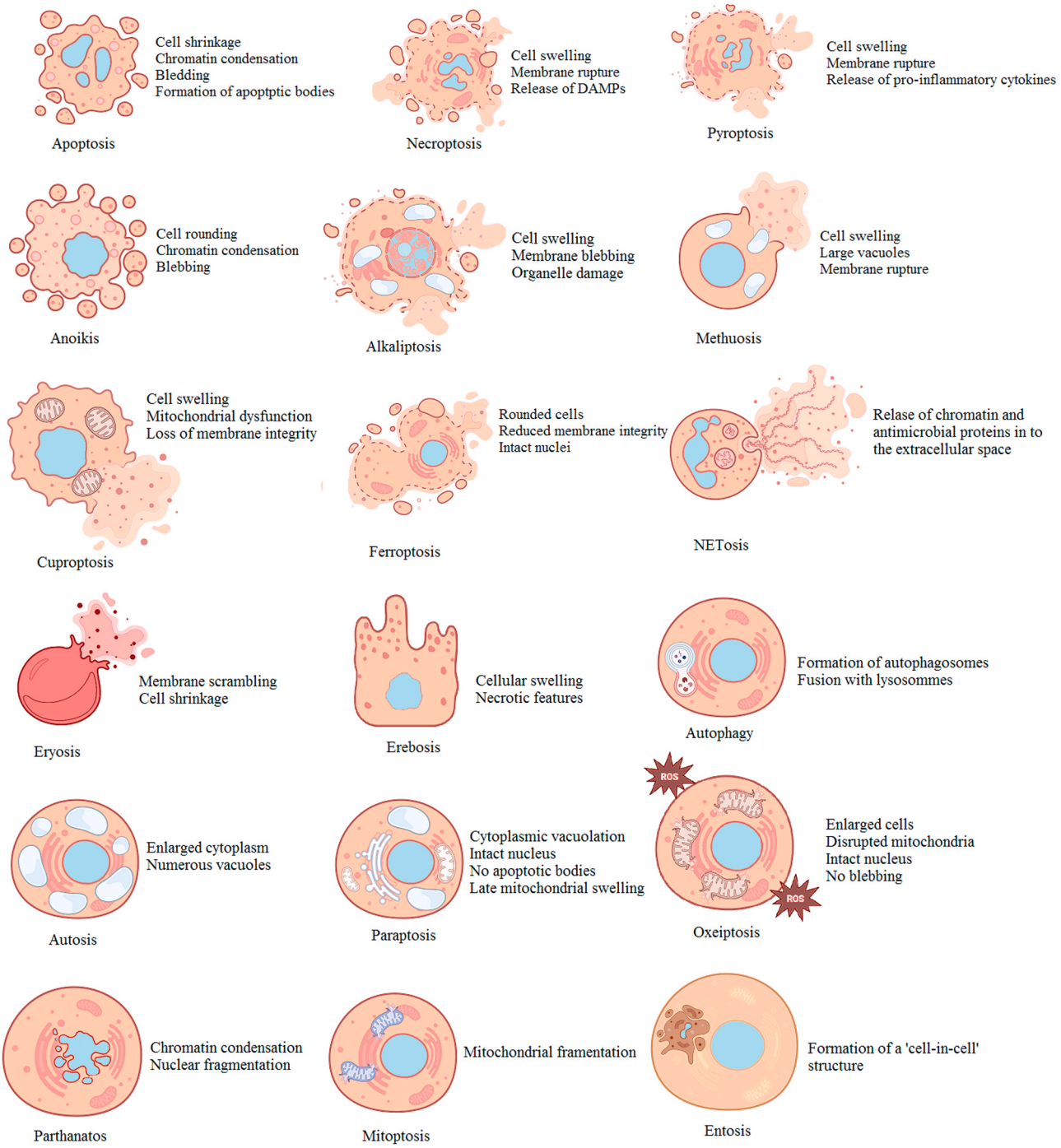

Fig. 1. Morphological features of various types of PCD. This figure illustrates the common morphological characteristics associated with different types of PCD, including chromatin condensation, nuclear fragmentation, membrane disruption, cytoplasmic swelling, and organelle breakdown. The image was created using BioRender.

coagulative necrosis resulting from gradual obstruction of blood flow, leading to dry, blackened tissue that often becomes mummified. In contrast, wet gangrene involves liquefactive necrosis due to bacterial infection, which results in swelling, pus formation, and a foul odor. Wet gangrene is particularly dangerous as it can spread rapidly and lead to systemic infections, potentially resulting in sepsis. Gangrenous necrosis is frequently observed in individuals with underlying health conditions such as diabetes mellitus or peripheral vascular disease, which compromise blood circulation and increase susceptibility to ischemic injury (Fink and Cookson, 2005; Adigun R and Murray, 2024).

2.1.7. Apoptotic/secondary necrosis

Apoptotic necrosis refers to a condition in which cells that have undergone apoptosis enter a state of secondary necrosis due to ineffective phagocytic clearance. This occurs when apoptotic cells are not adequately removed by macrophages or other phagocytes, resulting in cell rupture and the release of intracellular contents into the surrounding tissue. This release can trigger an inflammatory response, contributing to chronic inflammation and potential tissue damage. Secondary necrosis may arise in various pathological conditions, such as autoimmune diseases, certain cancers, and infections, where the clearance mechanisms are compromised (Adigun R and Murray, 2024; Karch and Molkentin, 2015).

2.2. Programmed cell death

PCD comprises various types, each characterized by unique signaling pathways that drive specific processes and mechanisms. These processes culminate in distinct morphological changes, as shown in Fig. 1. The following sections will delve into a detailed exploration of the eighteen types of PCD.

2.2.1. Autophagy

Autophagy, a vital self-digestive process, plays a crucial role in cellular maintenance. It facilitates the dismantling and recycling of cellular structures, including damaged organelles and misfolded proteins. Autophagy is essential for homeostasis, as it helps cells maintain their internal balance, ensuring that cellular components function optimally. By removing damaged or dysfunctional elements, autophagy also enables cells to better cope with stress and adapt to changing conditions. Furthermore, autophagy allows cells to switch to available nutrients, promoting survival during times of scarcity. In mammalian cells, this intricate process primarily occurs within lysosomes, where cellular debris is broken down and recycled (Yang and Klionsky, 2009; Aman et al., 2021).

Three main types of autophagy include macroautophagy, microautophagy and chaperone-mediated autophagy (CMA). Macroautophagy involves the formation of double-membrane vesicles, which can vary in size. Specifically, it includes the creation of vesicles larger than 1 μm as well as those measuring between 250 and 500 nm. This process generates a torus-shaped structure known as the autophagosome, which encases cellular structures before fusing with a lysosome for degradation. Microautophagy occurs when the lysosomal membrane folds inward to directly enclose cytoplasmic material. This process allows for the direct uptake of cellular components into the lysosome without the formation of an autophagosome. CMA is a selective process in which specific substrates are transported to the lysosome through interactions with chaperone proteins. CMA is regulated signal transduction pathways and is often induced under stress conditions, such as starvation or pathogen invasion (Shen et al., 2023a, 2023b; Parzych and Klionsky, 2014).

The autophagy process involves several distinct morphological changes, including formation of autophagosome from double-layered membranes that isolate cellular components destined for degradation. The autophagosomes then fuse with lysosomes, allowing the contents of the autophagosome to be degraded. Subsequently, lysosomal enzymes break down the materials inside the autophagosome into molecules that can be reused by the cell (Yang and Klionsky, 2009; Aman et al., 2021; Parzych and Klionsky, 2014). This complex process highlights the crucial role of autophagy in maintaining cellular homeostasis and facilitating stress adaptation. By recycling cellular components and providing building blocks for new molecules, autophagy ensures the efficient use of resources and the survival of cells under various conditions.

2.2.2. Apoptosis

Apoptosis is a vital biological process essential for maintaining organismal health by eliminating obsolete, unnecessary, or potentially harmful cells, including damaged, old, or virus-infected cells. It is particularly important during developmental processes, such as fetal development, where it facilitates the formation of distinct structures, like fingers and toes. This regulated cell death ensures proper tissue formation and overall homeostasis within the organism (Voss and Strasser, 2020). Moreover, apoptosis serves as a protective mechanism against diseases by eliminating potential cancerous cells. Aberrations in the regulation of apoptosis can lead to various health problems, such as cancer, where cells evade apoptosis and proliferate uncontrollably. Conversely, excessive or inappropriate apoptosis can contribute to neurodegenerative diseases and autoimmune disorders (Shen et al., 2023a; Ameisen, 2002).

Apoptosis can be initiated through two primary pathways: the intrinsic pathway and the extrinsic pathway. The intrinsic pathway is activated by intrinsic signal events, such as DNA damage or cellular stress signals, which lead to the release of cytochrome c from the mitochondria. This release activates caspases, which are proteases that can propel the cell death program. In contrast, the extrinsic pathway, which is known to be shorter than the intrinsic pathway, is initiated through activation by external signals. These signals involve the binding of death-inducing cytokines (for instance, TNF) to cell surface receptors. This pathway also leads to caspase activation and ultimately results in apoptosis (Shen et al., 2023a, 2023b).

Apoptosis is characterized by a series of distinct morphological transformations that facilitate the orderly dismantling of the cell. Initially, the cell undergoes shrinkage, reducing in size as it prepares for death, accompanied by the condensation of the cytoplasm. Within the nucleus, chromatin undergoes significant changes, including condensation and fragmentation into small, discrete pieces, which is a hallmark of the apoptotic process and essential for the dismantling of nuclear components. Concurrently, the cell membrane exhibits the formation of blebs—protrusions that appear on the surface of apoptotic cells—indicative of the underlying cytoskeletal changes. As apoptosis progresses, the cell ultimately disassembles into small membrane-bound fragments known as apoptotic bodies, which contain cellular components and are easily recognized by phagocytic cells. These apoptotic bodies are efficiently phagocytosed and cleared by neighboring phagocytic cells, such as macrophages, preventing the release of potentially harmful cellular contents into the surrounding tissue and avoiding the inflammatory responses typically associated with necrosis (Fink and Cookson, 2005; Shen et al., 2023b; Elmore, 2007).

2.2.3. Necroptosis

Necroptosis is a unique form of PCD that exhibits characteristics of both necrosis and apoptosis. Unlike apoptosis, which is a caspase-dependent process involved in programmed cell death, necroptosis is caspase-independent and occurs primarily in higher eukaryotic organisms. The apoptotic pathway that leads to necroptosis is primarily initiated by the activation of tumor necrosis factor (TNF) through its receptor, TNFR1. This interaction triggers the mobilization of various signaling proteins, including receptor-interacting protein kinase 1 (RIPK1), a molecular scaffold that can mediate either apoptosis or necroptosis depending on the cellular context. Upon activation, RIPK1 recruits receptor-interacting protein kinase 3 (RIPK3), leading to the

formation of a complex known as the necrosome. Within this complex, RIPK3 phosphorylates mixed lineage kinase domain-like protein (MLKL). Once phosphorylated, MLKL undergoes oligomerization and translocates to the plasma membrane, resulting in the disruption of membrane integrity and a controlled breakdown of the membrane. Consequently, DAMPs are released into the extracellular environment, triggering an inflammatory response (Ye et al., 2023a; Galluzzi et al., 2017). This process is marked by several necrotic features, including cell swelling, impaired mitochondrial function, and increased plasma membrane permeability, leading to the release of cytoplasmic contents into the extracellular environment. Necroptosis often serves as a backup mechanism when apoptosis is inhibited or when cells are unable to undergo apoptotic processes. When apoptosis is suppressed, necroptosis can be triggered by various stimuli, including death ligands and cytokines, which activate these kinases. The resulting cellular changes contribute to inflammation and tissue damage, distinguishing necroptosis from the more controlled and non-inflammatory nature of apoptosis (Fink and Cookson, 2005; Park et al., 2021; Dhuriya and Sharma, 2018).

During necroptosis, several distinct morphological changes occur that are characteristic of this process. Initially, the cell and its organelles undergo swelling due to the influx of water and ions, a hallmark of necrotic cell death. This swelling is followed by the disruption of the plasma membrane, leading to cell lysis, where intracellular contents are released into the extracellular environment (Seo et al., 2021).

2.2.4. Pyroptosis

Pyroptosis is a pathogen-induced form of inflammatory cell death that plays a critical role in the response to intracellular pathogens. This process is characterized by the activation of the inflammasome, a protein complex that triggers a cascade of signaling events. Pyroptosis serves as an effective barrier to facilitate rapid pathogen clearance and enhances the host immune response against infections (Bergsbaken et al., 2009). Pyroptosis involves several key steps, beginning with the formation of the inflammasome in response to intracellular stimuli, such as pathogen-associated molecular patterns (PAMPs) or DAMPs. This complex typically consists of pattern recognition receptors (PRRs) that detect these signals. Once formed, the inflammasome activates caspase-1, and in some instances, caspases 4, 5, or 11. Caspase-1 plays a crucial role in processing pro-inflammatory cytokines, such as IL-1β and IL-18, into their active mature forms. Additionally, caspase-1 cleaves gasdermin D, leading to oligomerization and the formation of pores in the plasma membrane, which disrupts ionic balance and causes cell swelling and eventual lysis. This process releases pro-inflammatory cytokines and other signaling molecules, enhancing the immune response and inflammation, thereby bolstering host defense against infections (Yu et al., 2021; Wei et al., 2022).

Pyroptosis is characterized by distinct morphological changes, including significant cell swelling due to the accumulation of water and ions, which increases osmotic pressure within the cell. The formation of gasdermin D pores results in plasma membrane rupture, contrasting with the controlled membrane blebbing observed in apoptosis. Additionally, chromatin condensation during pyroptosis differs from that in apoptosis; while the nucleus remains present, it often appears irregular in shape (Yu et al., 2021; Wei et al., 2022; Tan et al., 2021).

2.2.5. Paraptosis

Paraptosis is a type of PCD characterized by the swelling and vacuolization of the endoplasmic reticulum (ER) and mitochondria, leading to the formation of large cytoplasmic vacuoles. This caspase-independent process can be triggered by various factors, including proteasomal inhibition, altered protein thiol homeostasis, and unbalanced ion homeostasis. For instance, the accumulation of misfolded proteins within the ER due to proteasomal inhibition can lead to ER stress, which is a significant contributor to paraptosis. Additionally, disturbances in Ca^{2+} levels play a critical role in this process.

Key morphological features of paraptosis are lack of nuclear fragmentation, formation of large cytoplasmic vacuoles, swelling of mitochondria and the ER, cell shrinkage and disorganization of microtubules and release of danger signals, including high mobility group B-1 (HMGB1) and heat shock proteins, which contribute to inflammation (Kim et al., 2020; Hanson et al., 2023).

2.2.6. Ferroptosis

Ferroptosis is a unique form of cell death that is iron-dependent and characterized by lipid peroxidation, distinguishing it from apoptosis, necrosis, and autophagy. First reported in 2012, ferroptosis is marked by elevated levels of reactive oxygen species (ROS) and toxic lipid peroxides, which ultimately lead to cell death. This process has significant implications in various physiological and pathological conditions, including cancer and neurodegenerative diseases, highlighting its crucial role in cellular health and disease (Yan et al., 2021; Li et al., 2020; Hirschhorn and Stockwell, 2019).

Ferroptosis is initiated by the accumulation of iron, which catalyzes the production of ROS, thereby increasing oxidative stress within the cell. This process is characterized by the peroxidation of polyunsaturated fatty acids in membrane phospholipids, leading to the formation of toxic lipid peroxides that compromise membrane stability. The induction of ferroptosis is also contingent upon the disruption of antioxidant defense mechanisms within the cell, with particular emphasis on the glutathione-dependent antioxidant system. Glutathione peroxidase 4 (GPX4) is a well-known antioxidant enzyme that typically reduces lipid peroxides; its downregulation or knockout is essential for the activation of ferroptosis. Additionally, various signaling pathways and metabolic processes related to cysteine and lipid metabolism contribute to the regulation of this form of cell death (Yan et al., 2021; Li et al., 2020; Zhang et al., 2022).

Ferroptosis exhibits unique morphological features that distinguish it from other forms of cell death, such as apoptosis. Unlike apoptotic cells, which undergo shrinkage and fragmentation, ferroptotic cells may appear rounded without forming apoptotic bodies. In ferroptosis, mitochondria typically exhibit reduced size, increased membrane density, and a loss or absence of cristae, indicating cellular injury. In contrast to necrosis, where there is a conventional rupture of the plasma membrane, ferroptosis does not involve such rupture; however, it may lead to decreased membrane permeability and intracellular leakage. Notably, unlike apoptosis, ferroptosis does not display certain morphological characteristics, such as chromatin condensation and nuclear fragmentation; instead, the nuclear structure remains intact in ferroptotic cells, albeit often appearing irregular (Li et al., 2020; Hirschhorn and Stockwell, 2019; Zhang et al., 2022; Chen et al., 2021a).

2.2.7. Anoikis

Anoikis is a type of PCD that occurs in anchorage-dependent cells upon their detachment from the surrounding extracellular matrix (ECM). This process is essential for maintaining the balance and integrity of specific tissues, as it prevents detached cells from proliferating at undesired sites, which could potentially lead to tumorigenesis. The term "anoikis," derived from the Greek word for "*homelessness*", aptly describes the state of cells that have been expelled from the ECM, underscoring the critical importance of cell-ECM adhesion for cellular survival (Frisch, 2001; Wazir et al., 2015).

Anoikis involves a clear sequence of steps. First, when cells detach from the ECM, they lose the ability to utilize integrins, which are critical for growth factor signaling. This loss disrupts essential signal transduction pathways involved in cell growth and survival. As a result of detachment, various intracellular signals are activated, leading to the initiation of the apoptotic program, primarily mediated by caspases. This process is regulated by several signaling molecules, including pro-apoptotic proteins from the Bcl-2 family and death receptors. Additionally, anoikis is influenced by integrins, other matrix receptors, and signaling molecules associated with oncoproteins and tumor

suppressors. Notably, cancer cells can modify the mechanisms of anoikis, allowing them to survive after detachment and potentially metastasize to distant sites (Han et al., 2023; Adeshakin et al., 2021).

During anoikis, several distinct morphological changes occur, which can be categorized into specific phases or alterations. Similar to classical apoptosis, detached cells undergoing anoikis display characteristic morphological changes, including rounding and shrinkage of the cell body. This alteration in cellular morphology is accompanied by chromatin condensation, a well-established hallmark of apoptotic cell death, which is clearly evident in the nuclei of cells experiencing anoikis. As the process progresses, the plasma membrane may develop blebs, which are protrusions that form as the cell prepares for eventual division or disassembly. Ultimately, the cell may fragment into apoptotic bodies, which can be efficiently engulfed by neighboring cells or specialized immune cells, thereby preventing inflammation and minimizing tissue damage (Dai et al., 2023).

2.2.8. Entosis

Entosis is a unique cellular phenomenon that occurs in living cells, wherein a single cell penetrates the cytoplasm of another similar cell, thus creating a cell-in-cell (CIC) structure (the term "entosis" is derived from the Greek word meaning "*within*"). Entosis occurs when cells detach from the extracellular matrix (ECM) and internalize, particularly in epithelial cells and various cancers (Florey et al., 2015a; Kim et al., 2024). This process leads to significant alterations in cell function. The invading cell employs adhesion molecules and the actin cytoskeleton, which are regulated by the Rho family of GTPases, including RhoA, Rac1, and Cdc42. This mechanism facilitates the formation of adhesion bonds and the exertion of actomyosin contractility, allowing the outer cell to penetrate the inner cell. As a result, compartmentalization forms around the inner cell, a defining characteristic of entosis that differentiates it from other engulfment mechanisms, such as phagocytosis. The inner cell can have several potential fates: it may be degraded by autophagy, remain viable and capable of division within the host cell, or detach and re-enter the ECM (Florey et al., 2015b; Krishna and Overholtzer, 2016; Gaptulbarova et al., 2024).

As entosis is characterized CIC formation, it leads to significant morphological changes. The internalized cell undergoes shape alterations, becoming more rounded and compact. Initially, its nucleus remains intact; however, as entosis progresses, chromatin condensation and fragmentation occur. The cytoplasm of the engulfed cell may become vacuolated, and organelles can be degraded or reorganized. Ultimately, the internalized cell can be completely degraded, resulting in the loss of its nuclear structure and cytoplasmic components through lysosomal degradation (Kim et al., 2024; Gaptulbarova et al., 2024).

2.2.9. NETosis

NETosis is a form of PCD that results in the release of neutrophil extracellular traps (NETs), which are intercellular networks composed of neutrophil DNA along with antimicrobial peptides and enzymes. This process serves as an effective defense mechanism against infectious organisms, aiding in the immobilization and eradication of bacteria, fungi, and protozoa. NETosis can occur in two distinct forms: suicidal NETosis, in which neutrophils undergo apoptosis following the release of NETs, and vital NETosis, where neutrophils retain their functional capacity after the formation of NETs (Rada, 2019).

NETosis occurs through a series of sequential events, beginning with the activation of neutrophils in response to various stimuli, including pathogens, cytokines, and immune complexes. This activation triggers several intracellular signaling pathways that lead to the generation of ROS via NADPH oxidase. The activation of protein arginine deiminase 4 (PAD4) by ROS facilitates the citrullination of histones, resulting in chromatin dispersal and the merging of cytoplasmic granule proteins. Subsequently, the nuclear membrane is disrupted, allowing the release of NETs into the extracellular environment (Thiam et al., 2020).

NETosis is marked by notable morphological transformations in neutrophils. During this process, the nuclear envelope disintegrates, and chromatin undergoes condensation, which facilitates the mixing of nuclear DNA with cytoplasmic granule proteins. Neutrophils undergoing NETosis may also alter their shape, becoming round as they prepare to release NETs. The primary distinction between suicidal NETosis and vital NETosis is the condition of the plasma membrane. In suicidal NETosis, the plasma membrane is disrupted, resulting in the release of NETs and the death of the neutrophil. Conversely, in vital NETosis, the plasma membrane remains intact, allowing neutrophils to survive. The NETs released during this process form extracellular fibers predominantly made of DNA, combined with antimicrobial proteins and enzymes. These structures trap pathogens, effectively immobilizing them and aiding in their elimination by the immune system (Brinkmann et al., 2004; Delgado-Rizo et al., 2017).

2.2.10. Eryptosis

Eryptosis is a form of PCD that specifically affects erythrocytes in response to stressors such as hyperosmolarity, oxidative stress, energy depletion, and exposure to heavy metals. An increase in cytosolic Ca^{2+} is crucial for initiating eryptosis, as it activates potassium channels, leading to reduced intracellular potassium levels and subsequent cell shrinkage. Eryptosis plays a protective role by eliminating damaged or dysfunctional erythrocytes, however, excessive eryptosis can contribute to various pathological conditions, including anemia, malaria, and other hemolytic disorders. During this process, erythrocytes exhibit morphological alterations, including cell shrinkage, membrane blebbing, vacuolation, organelle reorganization and the externalization of phosphatidylserine on their surface (Lang et al., 2012; Pretorius et al., 2016; Alghareeb et al., 2023).

2.2.11. Parthanatos

Parthanatos is a unique form of PCD that involves several critical steps, beginning with DNA damage caused by various agents, including ROS, hydrogen peroxide, ionizing radiation, and alkylating agents. This damage prompts the overactivation of Poly (ADP-ribose) Polymerase 1 (PARP-1), which in turn leads to the formation and accumulation of PAR polymers. Subsequently, PAR binds to apoptosis-inducing factor (AIF), facilitating its release from the mitochondria. The AIF then translocates to the nucleus, where it forms a complex with macrophage migration inhibitory factor (MIF), ultimately causing large-scale DNA fragmentation that culminates in cell death. Parthanatos is implicated in a range of pathological conditions, particularly neurodegenerative diseases such as Parkinson's, Alzheimer's, Huntington's disease, and amyotrophic lateral sclerosis. Additionally, it plays a role in other health issues, including diabetes, stroke, heart attacks, and certain cancers (Liu et al., 2022; Huang et al., 2022a).

Parthanatos is marked by several morphological changes, including chromatin condensation akin to that observed in apoptosis. A key feature of parthanatos is mitochondrial swelling, indicating dysfunction and potentially leading to the release of pro-apoptotic factors. Additionally, there is a loss of plasma membrane integrity without the typical membrane blebbing associated with apoptosis, along with necrotic-like features resulting from the accumulation of PAR chains within the cytoplasm (Liu et al., 2022; Fatokun et al., 2014).

2.2.12. Mitoptosis

Mitoptosis, commonly known as mitochondrial suicide, is a form of PCD that is initiated by mitochondrial dysfunction and the production of ROS. This process can contribute to various diseases, including cancer and neurodegenerative disorders. The mitoptosis process begins with the fission of elongated mitochondrial structures into spherical forms, which then cluster in the perinuclear area, encapsulated by a membrane and form mitoptotic body. Within this body, the mitochondria decompose into smaller membrane vesicles, and ultimately, protrudes from the cell, resulting in the disruption of the cell's boundary membrane. Mitoptosis can manifest in different forms, including inner-membrane

and outer-membrane mitoptosis, depending on which components of the mitochondria are degraded. Mitoptosis does not utilize autophagic processes, and instead, it serves as a mechanism to eliminate dysfunctional mitochondria, thereby preventing cellular pathologies. Mitoptosis is characterized by distinct morphological features, including mitochondrial swelling and cristae remodeling, which can ultimately result in mitochondrial fragmentation (Jangamreddy and Los, 2012; Lyamzaev et al., 2020).

2.2.13. Methuosis

Methuosis is a newly recognized form of PCD that has gained prominence due to its unique characteristics and potential implications for cancer treatment. The name "methuosis" is derived from the Greek term "*methuo*", which translates to "to drink to intoxication," aptly describing the process's defining feature: the excessive accumulation of fluid within the cells. Initially identified in glioblastoma cells, methuosis has emerged as a crucial mechanism for non-apoptotic cell death, particularly in response to stimuli that promote macropinocytosis. This process is primarily activated through Ras signaling pathways and finally leads to the formation of large vacuoles within the cytoplasm. Unlike traditional apoptotic pathways, methuosis is characterized by dysfunctional endosomal trafficking; the vacuoles formed do not fuse with lysosomes, resulting in significant cytoplasmic swelling (Bielsa et al., 2022; Ye et al., 2023b).

The morphological changes characteristic of methuosis are marked by extensive cytoplasmic vacuolation that occupies much of the cytoplasmic content. Methuosis resembles necrosis, as it involves a loss of membrane integrity and a decline in metabolic function. This characteristic, along with the absence of nuclear fragmentation, distinguishes methuosis from other forms of PCD (Ye et al., 2023b; Maltese and Overmeyer, 2014; Overmeyer et al., 2011).

2.2.14. Autosis

Autosis is an emerging type of cell death that emphasizes the complex role of autophagy in cellular functions. It is defined as a non-apoptotic, autophagy-dependent mechanism associated with the dysregulation of autophagy under specific conditions, such as ischemia, starvation or severe stress (Bai et al., 2023; Fulda and Kögel, 2015). During autosis, the endoplasmic reticulum dilates and fragments, and the nuclear membrane may become convoluted. Cells undergoing autosis display several morphological changes, including swelling, membrane blebbing, and the accumulation of numerous autophagic vesicles, along with the degradation of organelles (Liu and Levine, 2015; Nah et al., 2020; Yang et al., 2024).

2.2.15. Alkaliptosis

Alkaliptosis represents a novel concept in the study of cell death, particularly regarding cellular responses to extreme environmental stress or metabolic dysregulation. This form of cell death is characterized by its association with alkaline pH and ion channel activity, highlighting the critical role of maintaining cellular homeostasis for overall health and function (Liu et al., 2020a; Chen et al., 2023). Alkaliptosis is triggered by an increase in intracellular pH, which disrupts ion balance and leads to significant cellular dysfunction. Consequently, cells undergoing alkaliptosis typically exhibit notable swelling and compromised membrane integrity, which can ultimately lead to cell rupture (Chen et al., 2024; Liu et al., 2020a; Chen et al., 2023; Que et al., 2023).

2.2.16. Oxeiptosis

Oxeiptosis is defined as a caspase-independent form of cell death triggered by ROS, highlighting the importance of maintaining redox homeostasis within cells. The involvement of specific signaling pathways, such as KEAP1-PGAM5-AIFM1, in mediating this form of cell death suggests that oxeiptosis may play a significant role in various pathological conditions, including neurodegenerative diseases and certain cancers. Oxeiptosis occurs when oxidative damage impacts various cellular components, leading to dysfunction and ultimately cell death through mechanisms distinct from both apoptosis and necrosis. This process may involve mitochondrial dysfunction, which further exacerbates oxidative damage. Cells undergoing oxeiptosis typically exhibit pronounced swelling, significant organelle damage, and loss of membrane integrity, which can ultimately lead to cell rupture (Park et al., 2023; Pallichankandy et al., 2023; Kang et al., 2022; Holze et al., 2018).

2.2.17. Cuprotosis

Cuprotosis is a newly recognized type of PCD that depends on copper ion overload, highlighting the delicate balance necessary for metal ion homeostasis within cells (Xing et al., 2024; Xie et al., 2023). Although the mechanisms underlying cuprotosis are still under investigation, it is clear that excessively high copper ions bind to mitochondrial proteins involved in the tricarboxylic acid (TCA) cycle. This binding leads to protein aggregation and subsequent downregulation of iron-sulfur cluster proteins, further exacerbating cellular stress. The morphological changes associated with cuprotosis include significant mitochondrial swelling and disruption, which can ultimately result in a loss of membrane integrity and necrotic features (Xing et al., 2024; Xie et al., 2023; Xiong et al., 2023; Vo et al., 2024; Tang et al., 2022).

2.2.18. Erebosis

Erebosis represents an intriguing advancement in our understanding of non-apoptotic cell death. The term "erebosis" is derived from the ancient Greek word "*erebos*", meaning "complete darkness", reflecting the obscure nature of this process and its mechanisms (Ciesielski et al., 2022; Bergmann, 2022). Erebosis plays a crucial role in maintaining tissue homeostasis, particularly in adult tissues such as the gut, where it facilitates the turnover of enterocytes without activating the apoptotic pathways typically associated with cell death. This process is linked to specific metabolic dysregulation, although the precise signaling pathways involved are still being elucidated. Morphological changes associated with erebosis include alterations in cellular architecture, loss of cytoskeletal integrity, disruption of cell adhesion, and organelle damage, along with the accumulation of specific proteins such as angiotensin-converting enzyme. Additionally, the nuclei of these cells may become flattened and difficult to discern, indicating a departure from typical cellular morphology (Ciesielski et al., 2022; Bergmann, 2022).

3. The crosstalk between various PCD pathways

Understanding the complexity and interconnectivity of PCD pathways may provide insights into therapeutic approaches that target multiple cell death pathways simultaneously to enhance treatment efficacy. Fig. 2 presents the physical and function network between the main regulatory proteins (nodes) involved in various types of PCD. As presented, the protein-protein interaction (PPI) network in STRING consisted of 31 nodes and 179 edges with enrichment p value $< 1.0e\text{-}16$. In the PPI network, all proteins are interconnected, exhibiting varying degrees of interactions. For example, P53 interacts with 18 nodes, including BAX, BCL-2, PARP1, GPX4, FADD, RIPK3 and caspases, underscoring the central role of P53 in apoptosis, autophagy and ferroptosis pathways. The Reactome pathway analysis identified "Regulated necrosis", "Programmed cell death" and "Pyroptosis" as significantly enriched pathways, with the false discovery rate (FDR) of 4.50e-19, 7.75e-17 and 4.53e-11, respectively. The gene ontology analysis for biological processes identified "Programmed cell death", "Programmed necrotic cell death", "Necroptotic signaling pathway" and "Pyroptosis" as significant terms with the FDR of 1.75e-15, 5.32e-09, 8.72e-07 and 2.62e-05, respectively. Additionally, KEGG pathway analysis revealed "Apoptosis", "Necroptosis" and "Ferroptosis" with FDR 1.10e-12, 1.12e-10 and 4.3e-4, respectively. The consistently low FDR values highlight the importance of these mediators in various cell

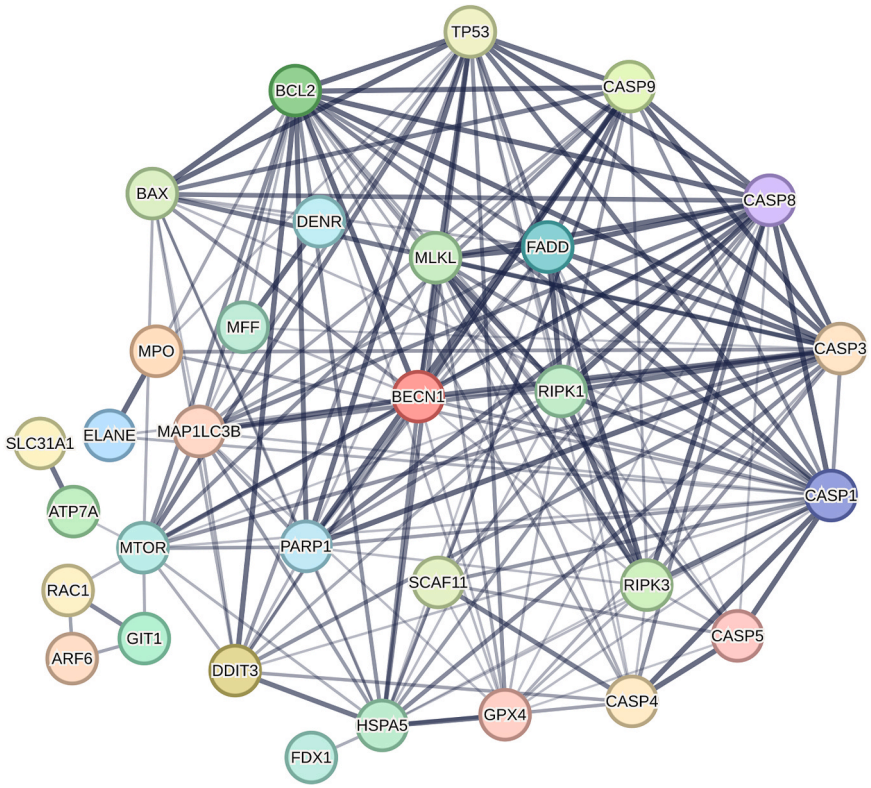

Fig. 2. The interconnections among the main proteins involved in various types of PCD were analyzed using a PPI network generated from the STRING database. This network comprised 31 nodes and 179 edges, illustrating both physical and functional interactions between proteins. The analysis highlights the complex relationships that exist among these proteins, providing insights into their roles in various cell death processes.

death mechanisms. Indeed, unraveling these enriched pathways provides insight into PCD and suggests promising opportunities for developing targeted therapies to modulate these pathways in various pathological conditions such as cancer.

In addition to the above computer-based analyses, there is substantial evidence highlighting the interconnectivity of PCD pathways, particularly among apoptosis, necroptosis, pyroptosis and autophagy. A crucial aspect of this crosstalk involves key regulatory proteins, notably caspases and RIPK3. Caspase-8 serves as a pivotal initiator in the extrinsic apoptotic pathway, which cleaves RIPK1 and RIPK3 upon activation, thereby inhibiting the necroptotic process. When caspase-8 is absent or inhibited, a necrosome complex forms, consisting of RIPK1 and RIPK3. This complex ultimately activates MLKL, leading to the execution of necroptosis (Dhuriya and Sharma, 2018; Morgan and Kim, 2022). While less studied than apoptosis and necroptosis, pyroptosis also interacts with these pathways. Pyroptosis is driven by inflammatory caspases, especially caspase-1, which cleave gasdermin D to create pores in the cell membrane. This process causes cell lysis and releases pro-inflammatory cytokines, enhancing inflammation. During immune responses, cells may switch from apoptosis to pyroptosis to boost inflammation and recruit immune cells more effectively (Bedoui et al., 2020; Wang et al., 2022). In contrast, autophagy often precedes apoptosis, illustrating a sequential relationship where autophagic processes can influence whether a cell undergoes apoptosis or necrosis, depending on the severity of cellular stress (Shen et al., 2023b). The interplay among these pathways is crucial in disease contexts. For example, in cancer, the activation of necroptosis can promote inflammation within the tumor microenvironment, potentially aiding tumor progression (Gong et al., 2019). Additionally, the intrinsic apoptotic pathway can be activated by signals that also trigger pyroptosis, suggesting that these pathways may cooperate to eliminate infected or damaged cells while modulating inflammatory responses (Lee et al., 2023).

4. Discussion and conclusion

This review provides a comprehensive overview of seven types of necrosis and eighteen forms of PCD, each type of characterized by molecular mechanisms, physiological functions and distinct morphological features. Understanding the differences and similarities between these cell death modalities is crucial for elucidating their roles in health and disease. ACD, exemplified by necrosis, is a pathological process resulting from injury or infection, characterized by cell swelling, membrane rupture and inflammation. Apoptosis and anoikis are caspase-dependent forms of PCD, while necroptosis proceeds through a caspase-independent pathway. Pyroptosis is triggered by inflammasome activation and the release of pro-inflammatory cytokines, whereas ferroptosis is driven by iron-dependent lipid peroxidation. Autophagy, a process of self-degradation, facilitates the recycling of cellular components, while entosis involves the internalization of one cell by another. Additionally, alkaliptosis, a pH-dependent form of PCD, oxeiptosis, a non-inflammatory variant induced by ROS, and autosis, a non-apoptotic process dependent on autophagy, are among the recently recognized types of PCD (Holze et al., 2018; Liu et al., 2020b). Despite their distinct features, most forms of PCD share some morphological similarities, such as chromatin condensation, membrane blebbing, and organelle damage. These commonalities underscore the complex interplay and potential crosstalk between various cell death pathways.

The dysregulation of PCD mechanisms significantly contributes to the pathology of both neoplastic and neurodegenerative diseases. Unraveling these processes opens avenues for therapeutic interventions aimed at restoring normal cell death pathways or targeting specific forms of cell death that are aberrantly regulated in these conditions. In human cancers, for instance, there is often an overexpression of the anti-apoptotic protein BCL-2, which can be effectively targeted by inhibitors such as venetoclax in the treatment of chronic lymphocytic leukemia (Del Poeta et al., 2016). Another instance is necroptosis in pancreatic

cancer, where it fosters inflammation in the tumor microenvironment, promoting tumor growth and metastasis (He et al., 2022). Additionally, certain cancer cells have been shown to manipulate lipid metabolism to avoid ferroptosis, indicating that promoting this pathway may improve the effectiveness of cancer therapies (Li and Li, 2020). For example, dihydroartemisinin can induce ferroptosis in squamous cell carcinoma of the head and neck, thereby inhibiting tumor growth (Lin et al., 2016). In the context of neurodegenerative diseases, mutations in the SOD1 gene impair the function of BCL-2, resulting in abnormal apoptosis of motor neurons in amyotrophic lateral sclerosis (Pedrini et al., 2010). Furthermore, in Huntington's disease, dysfunctional autophagy leads to the buildup of toxic protein aggregates, contributing to neuronal death (Cortes and La Spada, 2014). In Alzheimer's disease, amyloid-beta plaques can activate pyroptotic pathways in both microglia and neurons, triggering inflammation and exacerbating neuronal damage (Huang et al., 2022b).

Since dysregulated cell death plays a significant role in both cancer and neurodegenerative disorders, various clinical approaches aimed at restoring normal cellular functions or enhancing therapeutic efficacy. For instance, recent attempts have focused on targeting different forms of PCD, such as apoptosis, necroptosis, pyroptosis, and ferroptosis, to induce death in cancer cells that have developed resistance to conventional therapies using small-molecules (Peng et al., 2022; Tong et al., 2022). Exploiting the crosstalk between different cell death mechanisms is another strategy, which is based on combinatorial use of drugs to target multiple PCD pathways (Gong et al., 2023). Inducing mitotic catastrophe has also emerged as a promising approach, which targets cancer cells that have dysfunctional apoptotic machinery by promoting cell death through errors during mitosis (Mc Gee, 2015). Clinical applications in neurodegenerative disorders include inhibiting excessive apoptosis and/or promoting survival pathways to protect neurons from degeneration. In this regard, drugs that enhance the activity of pro-survival proteins from the BCL-2 family are being explored (Shacka and Roth, 2005). Moreover, therapeutic interventions that modulate ferroptosis may offer new avenues for treating conditions like Alzheimer's disease by preventing neuronal death associated with oxidative stress (Chen et al., 2021b).

Future research should focus on elucidating the molecular mechanisms underlying different forms of PCD and their interactions. This understanding may lead to the discovery of novel therapeutic strategies for restoring the balance between cell survival and death in disease states. Additionally, accelerating the understanding of the molecular mechanisms governing PCD will benefit significantly from interdisciplinary collaboration. The integration of bioinformatics and systems biology methodologies enables researchers to analyze extensive datasets, thereby identifying critical regulatory networks and signaling pathways implicated in PCD. Such collaborative initiatives can enhance our predictive capabilities regarding cellular responses to various therapeutic interventions and facilitate the development of targeted therapies that precisely modulate cell fate in pathological contexts.

CRediT authorship contribution statement

Fatemeh Behnam: Supervision. **Mohammad-Sadegh Lotfi:** Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the present work.

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Data Availability

No data was used for the research described in the article.

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