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A unified framework of cell death: Energy interdependence and multimodal interactions in disease pathogenesis

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Abstract

There are various cell death programs that require energy metabolism, redox balance, and the mitochondria–endoplasmic reticulum stress axis. These programs do not operate in isolation; they respond to microenvironmental changes. This review summarizes their networked organization and discusses how Adenosine Triphosphate balance, mitochondrial dynamics, and redox control shape death decisions. The paper also discusses how inflammatory signals integrate diverse modes of death, the diagnostic information contained in cross-death biomarkers, and why multi-target approaches are better suited to complex diseases.

Keywords: Cell death, energy metabolism, redox regulation, mitochondria–endoplasmic reticulum stress, multi-target interventions

Introduction

The latest discoveries in cell-death mechanisms like pyroptosis, apoptosis, ferroptosis, cuproptosis, and PANoptosis reveal a coherent network rather than isolated pathways [1]. Multi-omics and single-cell techniques indicate that these cell death programs affect important metabolic and stress nodes (energy balance, redox state, and the mitochondria–endoplasmic reticulum [ER] axis), and that they are shaped by metabolic pressure, inflammatory signals, and shifts in the microenvironment [2]. Under disease conditions, death pathways operate in parallel, compete with, or follow one another, thereby influencing intercellular communication and the overall immune and tissue responses. Viewing cell death as energy-dependent and multimodal enhances pathologic understanding and supports targeted interventions.

The network logic of cell death: Crosstalk, coupling, and feedback

Molecular nodes governing signaling interactions

Cell death signaling hinges on hub molecules that integrate metabolic stress, inflammation, and growth-factor signals. Klotho regulates ER–autophagy for tissue homeostasis. Interleukin-11 opposes the action of Signal Transducer and Activator of Transcription 1 and decreases reactive oxygen species (ROS) levels, blocking hepatocyte death induced by Interferon-gamma.

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Urolithin A induces ER stress and decreases signaling of the AKT mTOR–4EBP1 pathway—a cascade involving the kinase AKT, the mechanistic target of rapamycin (mTOR), and eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1)—to promote cell death through a different mechanism [3]. As these examples show, cell death relies on signal-integrating molecular nodes rather than linear pathways.

Pathway-level interaction models

Cell death pathways form interconnected networks centered on common axes. Visfatin affects both systemic glucose metabolism and the function of adipocytes. It also activates AMP-activated protein kinase and extracellular signal-regulated kinases 1 and 2 in pancreatic β cells, which prevents apoptosis. Ursolic acid blocks pyroptosis to reduce inflammation through the NF-κB–NLRP3–GSDMD axis (comprising Nuclear Factor Kappa B, NLR Family Pyrin Domain Containing 3, and Gasdermin D) [4]. Overall, the observations show that death pathways operate as modifiable interactive signaling systems rather than as linear causes.

System-level spatiotemporal coordination

Cell-death pathways are shaped by intracellular communication and the action of non-epithelial cells. Studies on mixed-target nanoplatforms have demonstrated the importance of targeting signaling in both tumor cells and tumor-associated macrophages. This approach can align innate and adaptive immunity and alter the dominant death programs in the tumor microenvironment [5]. This suggests that control over cell death is multilayered and constantly modulated by intercellular communication and microenvironmental cues. The major pathways and key nodes mapped in the molecular atlas are shown in **Figure 1**.

The foundational logic of cell death: Energy homeostasis and metabolic disassembly

Adenosine triphosphate (ATP) homeostasis and the turning points of death decisions

ATP plays a distinctly dual role in determining cell fate. Under normal physiological conditions, it ensures the requisite supply of energy. However, once ATP starts to accumulate abnormally outside the cell, its signaling shifts towards a pro-death mode almost immediately. Research has shown that increasing ATP causes breast cancer cells to die. Furthermore, under hypoxia stress, it induces even faster cell death while suppressing autophagy. The variations in ATP levels can also cause cell death. When ATP homeostasis is disrupted repeatedly, it marks a point of no return, leading to cell death.

Mitochondria: The energetic hub and resonance center of cell death

Mitochondria are not only the primary energy source of cells but also a key initiator of death pathways. When their balance is disturbed, there is often an escalation in metabolic dysfunction and death signaling. Palmitic acid damages mitochondrial DNA and the respiratory chain directly and renders myoblasts more death-prone. Since the electron transfer chain generates ATP and ROS, too much oxidative pressure can drive the crosstalk between apoptosis, ferroptosis, and other death phenotypes toward a convergent and amplifying response. The mitochondria-targeted compound CQ-Mito induces ferroptosis and apoptosis according to therapeutic studies, illustrating the organelle's important role in orchestrating multiple death programs [6]. Hence, mitochondria are not purely energy producers but key points where life or death diverge. **Figure 2** highlights the core nodes and regulatory signals through which mitochondrial dysfunction links energy imbalance to redox-driven cell death (apoptosis, autophagy, necroptosis, ferroptosis).

Integrated regulation within the redox network

The metabolic framework for cell death positions redox state at the tipping point between different death programs. ROS are not just amplifiers. They are also shared mediators that are used by many pathways. In pancreatic cancer, SRN-19 produces an accumulation of ROS and activates the p38 Mitogen-Activated Protein Kinase signaling pathway, which causes a concurrent enhancement of apoptotic and cytostatic responses [7]. As such, the redox network can be seen as a common regulatory axis for all forms of cell death. Redox dynamics connect metabolic imbalance with death-decision execution, thus providing a common molecular linkage among different death programs.

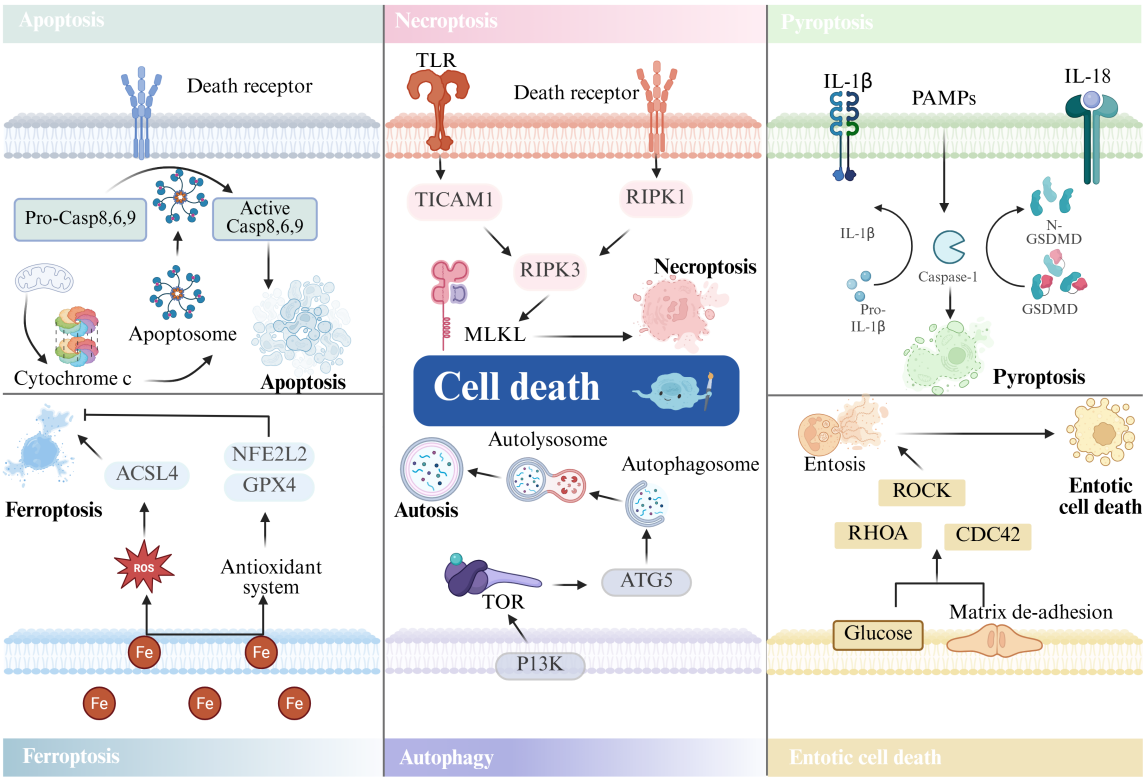

Figure 1. Molecular Atlas of Signaling Pathways and Key Molecules in Cell Death. This figure illustrates the molecular mechanisms of six cell death pathways: Apoptosis is initiated either via death receptors, activating Caspase-8, -6, and -9, or through cytochrome c release from mitochondria, forming apoptosomes; both pathways ultimately lead to programmed cell death; Necroptosis is triggered by TLR or death receptors, inducing necrosis-like cell death via the RIPK1-RIPK3-MLKL signaling pathway; Pyroptosis involves PAMPs activating Caspase-1, which then cleaves both GSDMD to form membrane pores and pro-IL-1β/IL-18 into their mature forms, resulting in inflammatory cell death; Ferroptosis is driven by iron ions inducing ROS accumulation, promoting lipid peroxidation via ACSL4, while the NFE2L2/GPX4 antioxidant system counteracts this process, leading to iron-dependent cell death; Autophagy is regulated by PI3K and TOR signaling, a process that controls autophagosome formation through proteins like ATG5 and culminates in the fusion of these autolysosomes with lysosomes, enabling the degradation of contents within autolysosomes; Entotic cell death occurs when glucose deprivation and matrix de-adhesion activate the ROCK-RHOA-CDC42 pathway, promoting cell entosis and subsequent death. Note: Casp, Caspase; TLR, Toll-like receptor; RIPK1, Receptor-interacting serine/threonine-protein kinase 1; RIPK3, Receptor-interacting serine/threonine-protein kinase 3; MLKL, Mixed lineage kinase domain-like pseudokinase; TICAM1, TIR-domain-containing adapter molecule 1; PAMP, Pathogen-associated molecular pattern; GSDMD, Gasdermin D; N-GSDMD, N-terminal fragment of Gasdermin D; IL-1β, Interleukin-1 beta; L-18, Interleukin-18; Fe, Iron ions; ROS, Reactive oxygen species; ACSL4, Acyl-CoA synthetase long-chain family member 4; NFE2L2, Nuclear factor erythroid 2-related factor 2; GPX4, Glutathione peroxidase 4; PI3K, Phosphatidylinositol 3-kinase; TOR, Target of rapamycin; ATG5, Autophagy-related protein 5; ROCK, Rho-associated coiled-coil-containing protein kinase; RHOA, Ras homolog family member A; CDC42, Cell division control protein 42.

Shared mechanisms and biomarkers across multiple cell death modalities

Convergence of inflammation and immune responses

Inflammation and immune activation share regulatory circuits. During β-coronavirus infection, the entry of the viral particle activates innate immunity and induces PANoptosis, a process in which the two pathways engage in a vicious cycle that drives the development of a cytokine storm. In cancers, though, persistent inflammation causes an exhaustion of $CD8^+$ T cells and weakens responses to immunotherapy, whereas Janus Kinase 1 inhibition externally reroutes T-cell differentiation and reinstates anti–Programmed Cell Death Protein 1 (PD-1) sensitivity [8]. These examples suggest that inflammatory signaling amplifies cell-death

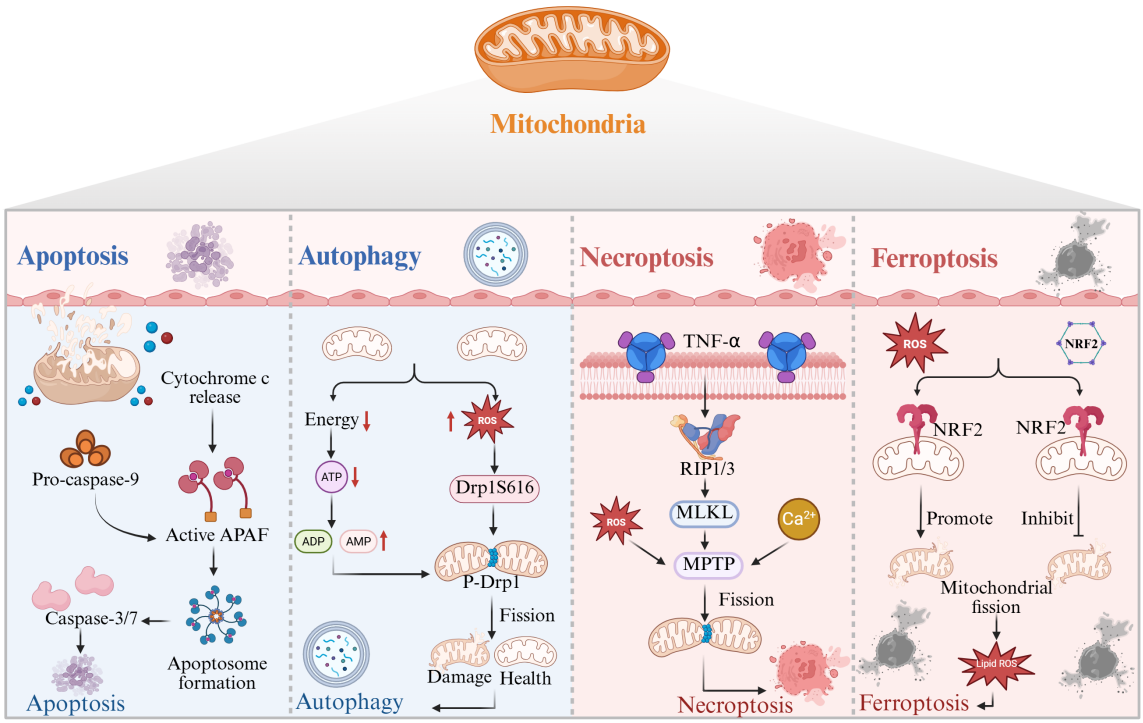

Figure 2. Mitochondria as a Central Node in Multiple Cell Death Pathways. This figure illustrates the central regulatory role of mitochondria in four cell death pathways: apoptosis, autophagy, necroptosis, and ferroptosis. In apoptosis, mitochondria release cytochrome c, which forms an apoptosome with pro-caspase-9 and others, activating Caspase-3/7 to induce cell death. In autophagy, changes in energy levels (decreased ATP, increased AMP), ROS, and others promote mitochondrial fission, and damaged mitochondria are degraded through autophagy to maintain intracellular homeostasis. In necroptosis, TNF-α signaling activates RIP1/3, which in turn regulates MLKL and MPTP; this process, along with changes in Ca^{2+} and production of ROS, promotes mitochondrial fission and ultimately triggers necroptosis. In ferroptosis, ROS activate NRF2, which can promote or inhibit mitochondrial fission, ultimately leading to ferroptosis through processes such as lipid peroxidation. Note: APAF, Apoptotic protease-activating factor; ATP, Adenosine triphosphate; ADP, Adenosine diphosphate; AMP, Adenosine monophosphate; TNF-α, Tumor necrosis factor-alpha; RIP1/3, Receptor-interacting serine/threonine-protein kinase 1/3; MLKL, Mixed lineage kinase domain-like pseudokinase; MPTP, Mitochondrial permeability transition pore; Drp1, Dynamin-related protein 1; p-Drp1, Phosphorylated Drp1; Drp1S616, Drp1 Serine 616; ROS, Reactive oxygen species; Ca^{2+}, Calcium ion; NRF2, Nuclear factor erythroid 2-related factor 2.

pathways and rewires immune behavior to create a common axis linking diverse death modes to immune dysfunction.

Coupling between mitochondrial and ER stress

ER and mitochondria act coordinately under stress. Macrophages undergo different mitochondrial changes in response to various nanoparticles. Some hyperpolarize with ER stress; others depolarize with high levels of ROS. Cell death relies on communication between the ER and mitochondria.

Likewise, in mechanical asphyxia, hypoxia induces C/EBP Homologous Protein, which subsequently translocates to the mitochondria and initiates apoptotic signaling. When these conditions are viewed together, they suggest something simple that often recurs. The coordinated stress of the ER and mitochondria is a common mechanism driving various cell death processes.

Reassessment of cross-death biomarkers

In a disease context, one cell-death program will often present an incomplete picture, because multiple cell-death programs coexist. Multi-omics and machine-learning techniques will bring cross-death features to the field. In glioma, a composite cell death signature can reflect tumor heterogeneity, immune status, and risk of drug resistance at the same time, outperforming individual markers associated with any

one mode of death. A similar trend appears in ischemic stroke. The analysis of the ferroptosis, heat-shock–related death, parthanatos, and cuproptosis pathways revealed sex-specific diagnostic markers: Solute Larrier Camily 2 Member 3 and Matrix Metallopeptidase 9 for men; Pyruvate Dehydrogenase Kinase 4 and Cluster of Differentiation 163 for women.

Determining diagnosis from single-pathway readouts may be limited. Findings suggest that cross-death biomarkers may provide a more accurate multi-modal framework for diagnosis.

Integrated intervention strategies: From single targets to system-level control

Limitations of traditional single-target approaches

Single pathway interventions face limitations. Blocking PD-1/Programmed Cell Death Ligand 1 has little utility for prostate cancer. However, coupling a therapeutic vaccine with checkpoint blockade broadens T-cell activation, bolsters T-cell infiltration, and overcomes resistance driven by the microenvironment. PARP inhibitors similarly impair tumor DNA damage repair, but can be detrimental to T cells, thereby compromising antitumor immunity. As standard cytotoxic therapies are largely unsuccessful due to the existence of long-lasting dormant tumor cells, it is essential to target autophagy and mTOR to eliminate the dormant survival state [9]. Based on these findings, one single switch to achieve tumor elimination while preserving immunity and reshaping the microenvironment will not be adequate. Thus, meaningful benefits will require more integrated multi-pathway strategies.

Potential of multi-target and multi-modal therapeutics

As different types of cancer cells behave differently and resistance against drugs becomes common in cancer treatment, the drugs that hit cancer cells from different targets are better than those just hitting a single target. One example is LCC-09. By blocking Dopamine Receptor D2/D4 and simultaneously suppressing AKT, mTOR and β-catenin signaling, it reverses temozolomide resistance and disrupts glioma stem-cell maintenance [10]. Sodium selenite in high doses puts pressure on cells in different ways. It causes a surge of ROS, lowers levels of glutathione and inhibits Glutathione Peroxidase 4, which together cause ferroptosis through oxidative stress and lipid peroxidation.

The findings suggest that broader regulatory leverage across metabolic and cell-death signaling networks could be expected from multi-target or multi-modal agents that fill an important gap left by single-target agents.

Contributions of artificial intelligence (AI) and network pharmacology

AI and network pharmacology offer a powerful approach for dissecting pathway interactions in the system-level intervention of complex diseases. Multi-omics techniques and molecular-docking analyses showed that DCH inhibits the Phosphatidylinositol 3-kinase/AKT/NF-κB axis and PANoptosis-related nodes, thereby improving sepsis-induced lung injury. Separately, puralne extra blocks AXL Receptor Tyrosine Kinase, mitigates ER stress, and induces immunogenic cell death. Overall, these examples signify a change. AI and networks are shifting drug discovery from single-target trial-and-error to system-wide, mechanism-based precision.

Discussion

According to recent studies, multiple cell-death programs seldom operate independently in disease. As a result, they point to a small set of metabolic and stress-response nodes—energy state, redox balance, and the mitochondria–ER interface. A change in these nodes due to metabolic or inflammatory pressures can drive death pathways to run in parallel, compete or trigger each other. Differences in ATP levels, mitochondrial stability, and inflammatory tone can help explain why diseases—and even patients—appear differentially susceptible to, and have different responses to, treatments. Therapeutically, this layered interplay limits the effects of single-target therapies. For example, in non-small cell lung cancer, the combination of Janus Kinase inhibition and PD-1 immunotherapy targets the redox-immune crosstalk and mitochondria-related death pathways, significantly improving patient response rates; in sepsis-induced lung injury, multi-target agents inhibiting the Phosphatidylinositol 3-kinase/AKT/NF-κB axis and PANoptosis-related nodes have shown promising therapeutic effects.

The use of multi-target agents, cross-death biomarkers, and AI-based network analyses offers more realistic ways to modulate the system as a whole. As the technologies behind single-cell, spatial-omics and live-imaging mature, they may help chart these death networks at improved resolution, enabling true system-level precision interventions.

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