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COMMENTARY

# Apoptosis and pyroptosis: Precision engineering of dual cell death modalities for therapeutic reprogramming

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Received: June 30, 2025; Accepted: November 19, 2025; Published Online: November 20, 2025; https://doi.org/10.59717/j.xinn-life.2025.100173



Citation: Zheng C., Fu Y., Gao Y., et al. (2025). Apoptosis and pyroptosis: Precision engineering of dual cell death modalities for therapeutic reprogramming. *The Innovation Life* **3**:100173.



The pursuit to decipher how distinct modes of regulated cell death be precisely controlled and harnessed for immune modulation and tissue regeneration remains a central challenge in translational medicine. Among these, apoptosis and pyroptosis exemplify two fundamentally divergent yet complementary programs, the former ensuring immunologically silent clearance *via* cellular dismantling, while the latter provokes robust inflammatory activation through lytic disassembly. These opposing outcomes shape diverse pathological processes, with excessive apoptosis leading to degenerative or immunosuppressive conditions, whereas uncontrolled pyroptosis drives autoinflammatory processes and exacerbates the pathogenesis of infectious diseases. For years, it has become increasingly clear that these death programs influence tissue regeneration beyond immunity, although the principles governing their pleiotropic functions remain incompletely defined. Recent conceptual advances now suggest that the specificity of these effects is dictated not only by the molecular control of the death process itself but also by the lineage identity of the dying cell, both of which define the composition of death-associated cargo and thereby shape immune and reparative outcomes. This emerging view reframes cell death as an active, lineage- and context-dependent form of molecular communication rather than a passive terminal event. Accordingly, engineering apoptotic and pyroptotic programs within defined cell lineages offers a tractable strategy to program immune and regenerative responses with precision, though current understanding remains limited by the incomplete mapping of death-mode outputs across tissues and disease settings. Future work will need to establish high-resolution atlases of death-mode output and develop tools to precisely modulate death programmes *in situ* for therapeutic reprogramming.

**ADVANCING MECHANISTIC INSIGHTS AND PRECISION REGULATION OF APOPTOSIS AND PYROPTOSIS FOR THERAPEUTIC REPROGRAMMING.** The emerging paradigm posits that both apoptotic and pyroptotic cells function as lineage-specific signal hubs, defined by unique death-associated molecular patterns that are distinct from their living state and thereby directly instruct immune and reparative outcomes.[1,2] Apoptotic clearance is now understood as a discriminative process in which the origin of apoptotic cargo determines macrophage polarization from tissue remodeling to tolerogenesis, rather than as a uniformly suppressive event. In specific, Liebold *et al.*[1] found that macrophages exhibited varying signatures depending on the type of apoptotic cell they encountered (Figure 1A). Engulfment of apoptotic neutrophils prompted a tissue remodeling profile in an interleukin-4 (IL-4)-enriched environment, whereas efferocytosis of apoptotic hepatocytes promoted an immunosuppressive or tolerogenic phenotype.[1] In contrast, the uptake of apoptotic thymocytes minimally altered macrophage responses.[1] This cell-type–dependent immunomodulation highlights an evolutionary strategy for aligning immune tone with tissue composition, while simultaneously generating heterogeneity whose mechanistic origins remain unresolved. This complexity also unveils an opportunity in which precise modulation of apoptotic programs within defined cellular subsets may enable therapeutic reprogramming, leveraging selective efferocytic cues to resolve inflammation or promote tissue repair in a controlled manner.

Parallel breakthroughs in pyroptosis research further dismantle the dogma that lytic cell death is exclusively detrimental. Mehrotra *et al.*[2] utilized a system where macrophages undergo pyroptosis without releasing IL-1α and IL-1β (designated as Pyro$^{-1}$), revealing unanticipated benefits associated with the Pyro$^{-1}$ secretome (Figure 1B). They initially revealed that Pyro$^{-1}$ supernatants markedly elevated gene signatures linked to migration, cellular proliferation and wound healing.[2] This enhancement corresponded with increased migration of primary fibroblasts and macrophages, resulting in accelerated wound closure *in vitro* and enhanced tissue repair *in vivo*.[2] Furthermore, mechanistic analyses involving lipidomics and metabolomics of Pyro$^{-1}$ supernatants underscored that the oxylipins and metabolites mediated the pro-wound-healing effects.[2] This functional decoupling between lytic death and inflammatory output suggests that pyroptosis can adopt context-dependent states that support physiological repair, highlighting that the reparative legacy of dying cells depends not only on lineage identity but also on death-associated molecular patterns. However, a central challenge remains how to systematically decode this death signaling and harness it therapeutically without triggering aberrant inflammatory responses or disrupting tissue homeostasis. Addressing this will require mapping the spatiotemporal dynamics of death-derived cues in diverse microenvironments and developing tools to precisely tune the initiation, execution, and clearance of cell-death programs *in vivo*.

**SYNTHETIC AND ENGINEERING CONTROL OF APOPTOSIS AND PYROPTOSIS FOR THERAPEUTIC STRATEGIES.** Building on these mechanistic insights, the next challenge lies in translating understanding into engineering control of apoptotic and pyroptotic programs. Achieving such precision control remains difficult, as manipulating when, where, and how a cell dies—while avoiding collateral inflammation—requires tools with molecular specificity, temporal resolution, and contextual adaptability. To be noted, current approaches using death ligands, chemogenetics, optogenetics, *etc.*, typically restrict cell death to a single mode or leave the choice to the target cell, lacking active control over cell death pathways and resulting in unintended consequences, which limits their application in other organs/diseases. In this sense, regulated cell death is shifting toward an engineering discipline, akin to synthetic biology, where death programs are no longer passively observed but purposefully designed. For example, Xia *et al.* recently developed synthetic apoptosis-pyroptosis ("synpoptosis") circuits that employ protease-based logic to bidirectionally regulate executioner proteins, enabling reversible control over apoptotic and pyroptotic outcomes (Figure 1C).[3] These engineered systems finely tune the apoptosis-pyroptosis balance, selectively eliminating pathogenic cells while sparing healthy tissue, and offer a versatile framework for diseases driven by dysregulated cell death, such as cancer, fibrosis, and chronic infection. However, current designs remain largely restricted to immortalized cell lines and overlook hybrid programs like necroptosis and ferroptosis, highlighting the challenge of achieving context-aware, multimodal death control *in vivo*.

Equally critical is the challenge of decoding and redesigning the molecular cargo released by dying cells. Among diverse death-associated products, vesicles have emerged as particularly compelling targets for therapeutic engineering. Their biogenesis intrinsically couple membrane dynamics, molecular sorting, and bioactive cargo assembly, providing a natural platform for programmable self-organization and delivery. Recent studies show that extracellular vesicles (EVs) released during distinct modes of regulated cell death exhibit unique molecular features. Among them, apoptotic vesicles (apoVs) derived from apoptosis and pyroptotic vesicles (pyroVs) originating from pyroptotic cells carry lineage- and death-mode-specific molecular signatures distinct from EVs of living cells. Leveraging this endogenous complexity, engineered derivatives of apoVs and pyroVs are being developed to expand their therapeutic versatility, from hybrid apoptotic vesicles integrating nanomaterials for enhanced bioactivity, to pyroptotic vesicle-based vaccines enriched in tumor antigens and inflammasome-associated signals that stimulate robust antitumor immunity (Figures 1D-E).[4,5] They demonstrate significant therapeutic promise in immune-related disorders and tissue repair, spurring the development of engineered variants to enhance their functional versatility and expand the translational potential of apoptotic/pyroptotic cell-derived products. However, fundamental questions remain unresolved regarding the plasticity of these vesicles. How their cargo composition dynamically adapts to tissue injury contexts, orchestrates spatial immune reprogramming, or reconciles paradoxical outcomes across microenvironments. Systematic mapping of vesicle biogenesis to metabolic/epigenetic recipient cell states will be critical to harness their therapeutic potential.

**CONCLUDING REMARKS.** The advancement of cell death mechanisms and modulation techniques holds transformative potential in translational medicine. Recent discoveries deepen mechanistic understanding while providing tools to reshape cell death control, yet significant challenges impede clinical translation. Cell death pathways exhibit remarkable plasticity, with apoptosis and pyroptosis displaying context-dependent roles shaped by the microenvironment. This variability underscores the need for precise

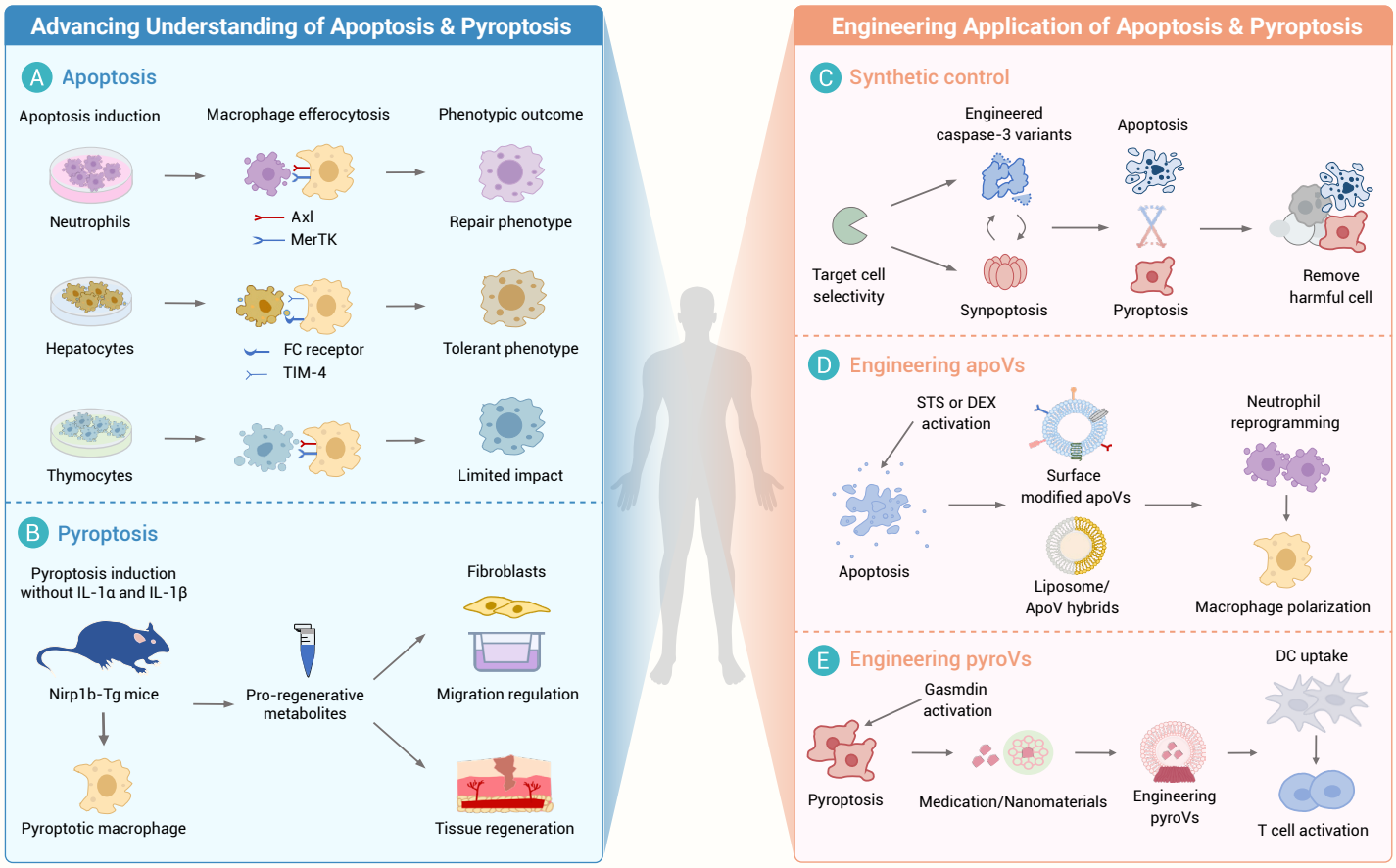


**Figure 1. Precise regulation strategies of apoptosis and pyroptosis for therapeutics** (A) Apoptotic cell identity shapes macrophage responses *via* lineage-specific receptors: neutrophil apoptosis activates Axl/MerTK to drive repair, hepatocyte apoptosis engages FcRs/TIM-4 to induce tolerance, while thymocyte apoptosis triggers minimal activation. (B) Macrophages from Nlrp1b-Tg mice undergo IL-1α/β–independent pyroptosis, releasing oxylipins/metabolites that potentiate fibroblast activation and regeneration. (C) Synthetic circuits program cell death *via* engineered caspase-3 variants, enabling controlled apoptosis, pyroptosis, or synpoptosis for selective cell elimination. (D) STS/DEX-induced apoVs can be engineered *via* surface modification or liposome hybridization to modulate neutrophil reprogramming and macrophage polarization. (E) Engineered pyroVs generated by gasdermin activation and functionalized with nanomaterials/drugs enhance DC uptake and T-cell activation. Abbreviations: Axl, Axl receptor tyrosine kinase; MerTK, MER proto-oncogene tyrosine kinase; FcRs, Fc fragment–binding receptors; TIM-4, T-cell immunoglobulin and mucin-domain containing-4; *Nlrp1b*-Tg, NLR family pyrin domain containing-1B transgenic mice; STS, Staurosporine; DEX, Dexamethasone; DCs, Dendritic cells; GSDM, Gasdermin; Synpoptosis, Synthetic apoptosis–pyroptosis hybrid form.

control over execution programs to balance immune modulation and tissue remodeling. It must be addressed the heterogeneity of apoptotic and pyroptotic products, which inherit molecular signatures from their parent cells. On the other hand, since these death products reflect the state of their originating cells, any instability, such as malignant transformation, could pose safety risks. Moreover, interactions among programmed cell death (PCD) modes remain poorly understood. Crosstalk between apoptosis, pyroptosis, necroptosis, and ferroptosis may produce unexpected cascade effects, challenging the predictability of engineered systems *in vivo*.

From a translational perspective, scalable production, purification, quality control of engineered or synthetic death control, and tissue-specific delivery remain major technical barriers. In parallel, ethical frameworks governing therapeutic manipulation of cell death are still underdeveloped, necessitating rigorous evaluation of biosafety, immunogenicity, and long-term host integration under clinically compliant standards. Looking forward, early translational opportunities may arise in immune-mediated and degenerative disorders, which represent feasible entry points for first-in-human applications and proof-of-concept trials. Integrating cutting-edge technologies like high-throughput sequencing, synthetic biology, and gene editing promises to address current limitation and expedite the clinical translation of cell death modulation strategies. As these technologies mature, reprogramming cell death may evolve from a conceptual possibility into a clinically actionable paradigm-transforming cellular demise into a new frontier for regenerative and precision medicine.

**Declaration of generative AI and AI-assisted technologies in the writing process.** During the preparation of this work the authors used DeepSeek in order to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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## FUNDING AND ACKNOWLEDGMENTS

This work was supported by grants from the National Natural Science Foundation of China (82170988, 82301028 and 82371020), the Project of State Key Laboratory of Oral & Maxillofacial Reconstruction and Regeneration (2024MS04 and 2024KA01), the Shaanxi Provincial Health Research and Innovation Platform Construction Plan (2024PT-04) and the China Postdoctoral Science Foundation (BX20230485). We thank the lab member Jianing Liu for helping to prepare the manuscript. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

## DECLARATION OF INTERESTS

The authors declare no competing interests.