

## Unlocking Cell Death: Advances in Targeting Necroptosis, Pyroptosis, Ferroptosis, and Cuproptosis for Cancer Therapy

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### Abstract

Various human cells undergo self-destruction to uphold biological equilibrium and safeguard the body against pathogens, a phenomenon known as regulated cell death (RCD). Among these processes, apoptosis has long been a focal point due to its role in clearing aberrant cells. However, tumor cells often evade apoptosis, leading to treatment resistance and recurrence. Consequently, researchers have turned their attention to alternative RCD pathways, including necroptosis, pyroptosis, ferroptosis, and cuproptosis, which have emerged as pivotal targets in cancer therapy. These alternative RCD pathways have been extensively studied for their potential to overcome treatment resistance and enhance therapeutic effectiveness. Moreover, evidence suggests that cancer cells undergoing regulated death can modulate the tumor microenvironment (TME), potentially impeding cancer progression and metastasis. Additionally, other components of the TME undergo these forms of cell death, prompting immune responses against tumor cells and bolstering antitumor activities.

### Introduction

In the realm of cancer therapy, the traditional focus has been on inducing apoptosis, the well-known programmed cell death mechanism. However, emerging research has illuminated alternative cell death pathways, including necroptosis, pyroptosis, ferroptosis, and cuproptosis, as potential targets for novel anticancer strategies. This article explores recent advances in understanding and harnessing these alternative cell death pathways for precision cancer therapy. This review delves into the molecular intricacies and characteristics of necroptosis, pyroptosis, ferroptosis, and cuproptosis, elucidating their impact on tumor cell proliferation and metastasis. It highlights how these novel RCD modalities influence the TME and the regulated death of surrounding cells, shaping tumor biology [1]. Furthermore, it summarizes the agents and nanoparticles capable of inducing or inhibiting these RCD pathways, drawing on evidence from both in vivo and in vitro studies, as well as clinical trials evaluating RCD inducers as cancer treatments. The review also examines the implications of modulating RCD processes on cancer drug resistance and discusses the advantages of integrating RCD modulators into cancer treatment regimens compared to conventional therapies. By elucidating the multifaceted effects of alternative RCD pathways on cancer biology and treatment outcomes, this review aims to shed light on novel avenues for improving cancer therapy and overcoming treatment challenges in clinical practice.

### Necroptosis: a programmed necrosis pathway:

Necroptosis, a form of programmed necrosis, has garnered attention as a potential therapeutic target due to its immunogenic nature and its ability to bypass apoptosis resistance mechanisms in cancer cells [2]. Key players in necroptosis include receptor-interacting protein kinases (RIPKs) and mixed lineage kinase domain-like protein (MLKL). Recent studies have identified small molecule inhibitors targeting RIPK1 and RIPK3 as promising candidates for inducing necroptosis in cancer cells, offering a novel approach to overcome therapy resistance.

### Pyroptosis: inflammatory cell death:

Pyroptosis is an inflammatory form of programmed cell death triggered by inflammasome activation and caspase-1-mediated cleavage of gasdermin proteins [3]. This process leads to cell swelling,

membrane rupture, and release of pro-inflammatory cytokines, promoting immune responses against cancer cells. Targeting the inflammasome or gasdermin proteins presents a novel strategy for inducing pyroptosis in cancer cells, potentially enhancing the efficacy of immunotherapy and immune checkpoint inhibitors.

### Ferroptosis: iron-dependent cell death:

Ferroptosis is characterized by iron-dependent lipid peroxidation and oxidative stress, leading to cell membrane damage and cell death. Dysregulation of iron metabolism and antioxidant defense mechanisms can render cancer cells vulnerable to ferroptosis induction. Small molecule inhibitors targeting key regulators of ferroptosis, such as glutathione peroxidase 4 (GPX4) and system Xc<sup>-</sup> cystine-glutamate antiporter, have shown promise in preclinical studies as potential anticancer agents, particularly in tumors resistant to conventional therapies.

### Cuproptosis: copper-mediated cell death:

Cuproptosis, a recently discovered form of regulated cell death, is triggered by dysregulation of copper homeostasis and oxidative stress. Copper accumulation in cancer cells can induce cuproptosis, leading to mitochondrial dysfunction, DNA damage, and cell death [4]. Targeting copper transporters and chelating agents offer new avenues for selectively inducing cuproptosis in cancer cells while sparing normal tissues.

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## Molecular mechanisms of different cell death pathways

### Apoptosis:

- Apoptosis, also known as programmed cell death, is characterized by a series of well-defined molecular events.
- It involves the activation of caspase enzymes, which serve as the central executioners of apoptosis.
- There are two main pathways of apoptosis: the intrinsic (mitochondrial) pathway and the extrinsic (death receptor) pathway.
- In the intrinsic pathway, various intracellular stress signals lead to mitochondrial outer membrane permeabilization (MOMP), releasing cytochrome c into the cytoplasm, which triggers the formation of the apoptosome complex and subsequent caspase activation.
- The extrinsic pathway is initiated by the binding of death ligands (e.g., Fas ligand, TNF- $\alpha$ ) to death receptors on the cell surface, leading to the activation of caspase-8 and downstream caspase cascade.
- Both pathways converge at the activation of effector caspases, which cleave key cellular substrates, leading to characteristic morphological changes associated with apoptosis, such as chromatin condensation, DNA fragmentation.

## Clinical implications and future directions

The therapeutic potential of targeting alternative cell death pathways, including necroptosis, pyroptosis, ferroptosis, and cuproptosis, holds promise for overcoming resistance to traditional cancer treatments and improving patient outcomes. However, further research is needed to elucidate the complex molecular mechanisms governing these cell death pathways and to optimize therapeutic strategies for clinical translation [5-8]. Combination approaches targeting multiple cell death pathways or integrating them with existing treatment modalities, such as chemotherapy, radiation therapy, and immunotherapy, may enhance efficacy and minimize resistance in cancer treatment.

## Conclusion

In conclusion, the elucidation of alternative cell death pathways has opened new avenues for precision cancer therapy. Harnessing necroptosis, pyroptosis, ferroptosis, and cuproptosis as therapeutic targets offers exciting prospects for overcoming treatment resistance and improving patient survival in various cancer types. Continued research efforts aimed at deciphering the intricacies of these cell death mechanisms and translating them into clinical applications will be essential for realizing their full therapeutic potential in oncology.

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