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Programmed cell death as a therapeutic target in cancer and diabetic nephropathy

Estrella-Rubí-Frausto-De la Cruz [1,*], Marco-Antonio-Jiménez-López [2] and Emiliano-Candelas-González [1]

[1] *Student at the Autonomous University of Durango, Zacatecas Campus, Zacatecas, Zacatecas, Mexico.*
[2] *Professor at the Autonomous University of Durango, Zacatecas Campus, Zacatecas, Zacatecas, Mexico.*

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Abstract

Cell death is an essential process for homeostasis and defense against external threats. Its main forms—apoptosis, necroptosis, pyroptosis, autophagy, and PANoptosis—have been shown to play a key role in the pathophysiology of diseases such as cancer and diabetic nephropathy. A systematic literature search was conducted in PubMed between January 2022 and May 2025, using keywords related to apoptosis, necroptosis, pyroptosis, PANoptosis, immunogenicity, cancer, and diabetic nephropathy. Review articles and original articles with access to the full abstract, published in English and Spanish, were included. Eleven articles were selected, ranging from the basic molecular mechanisms of MCP to their clinical and therapeutic implications. The findings highlight the role of DAMPs and ubiquitination as regulators of immunogenicity and cellular signaling. In cancer, necroptosis and PANoptosis emerge as immunogenic pathways capable of enhancing immunotherapy. Additionally, small-molecule compounds and natural plant derivatives with the ability to modulate apoptosis, necroptosis, and autophagy were identified.

In diabetic nephropathy, the combination of apoptosis, necroptosis, and insufficient autophagy accounts for much of the progressive kidney damage. Taken together, targeted modulation of the MCP represents a promising therapeutic strategy in cancer and diabetic nephropathy, opening up new opportunities to improve clinical efficacy and patients' quality of life.

Keywords: Apoptosis; Necroptosis; Cancer; PANoptosis; Diabetic nephropathy; Immunogenicity

1. Introduction

Programmed cell death (PCD) is an essential process for maintaining tissue homeostasis and defending against external threats. Its main forms include apoptosis, necroptosis, pyroptosis, and autophagy-dependent cell death, each with specific yet interconnected molecular mechanisms. Understanding of these pathways has evolved over the past few decades, revealing their role not only in physiological development but also in the pathogenesis of various diseases.

In the field of cancer, evasion of the immune system is one of the defining characteristics of tumor cells, promoting uncontrolled proliferation and resistance to treatment. Necroptosis and PANoptosis have gained particular relevance due to their ability to induce antitumor immune responses, opening new avenues in immunotherapy. Furthermore, the identification of small-molecule compounds and natural plant derivatives capable of modulating these pathways offers opportunities for the development of more effective and personalized therapies.

On the other hand, in diabetic nephropathy, apoptosis of podocytes and tubular cells, along with impaired autophagy and the activation of necroptosis, contribute decisively to progressive kidney damage. These findings suggest that manipulating the MCP could become a therapeutic strategy to preserve kidney function in diabetic patients.

* Corresponding author: Estrella-Rubí-Frausto-De la Cruz.

In this context, the aim of this study is to review the mechanisms, functions, and clinical implications of apoptosis, necroptosis, pyroptosis, and PANoptosis, as well as to explore the therapeutic opportunities arising from their modulation in cancer and diabetic nephropathy.

2. Materials and Methods

A systematic literature search was conducted in the PubMed database between January 2022 and May 2025. The following keywords were used: apoptosis, necroptosis, pyroptosis, PANoptosis, programmed cell death, immunogenicity, cancer, and diabetic nephropathy.

The inclusion criteria were:

- -Review articles and original articles published in English or Spanish.
- -Publications with access to the full abstract.
- -Studies addressing molecular mechanisms, regulation, or clinical or therapeutic implications of apoptosis, necroptosis, pyroptosis, autophagy, and PANoptosis.

The exclusion criteria were:

- Publications without access to an abstract.
- Duplicate studies.
- Articles not directly related to programmed cell death pathways.

After applying these criteria, 11 articles were selected, ranging from the basic molecular mechanisms of apoptosis and necroptosis to their implications in cancer, diabetic nephropathy, and emerging therapies using small-molecule compounds and natural plant derivatives.

3. Results and Discussion

3.1. Fundamentals of Programmed Cell Death

Programmed cell death (PCD) is an essential process for the homeostasis and development of multicellular organisms. Its main forms include apoptosis, necroptosis, and pyroptosis, each with specific molecular mechanisms but also with shared components. Apoptosis is characterized by caspase activation and regulation by the Bcl-2 family, leading to an orderly, non-inflammatory elimination of damaged cells [3]. In contrast, necroptosis depends on the activation of RIPK1, RIPK3, and MLKL, resulting in a form of programmed necrosis with the release of pro-inflammatory signals [5]. Pyroptosis, on the other hand, is triggered by the activation of caspases that cleave gasdermins, allowing the formation of pores in the plasma membrane and the release of inflammatory mediators [5].

Despite their differences, these pathways are functionally interconnected, sharing common molecular actors and regulators. This interrelationship suggests that the MCP should not be viewed as isolated processes, but rather as a highly coordinated system that responds to various physiological and pathological contexts [2]. Understanding these similarities and differences is crucial for designing therapeutic strategies aimed at manipulating cell death in diseases such as cancer and inflammatory conditions.

3.2. Molecular Regulation and Post-Translational Modifications

The immunogenicity of cell death depends not only on the activated pathway but also on the damage-associated molecular patterns (DAMPs) released during the process. These endogenous molecules—proteins, lipids, and nucleic acids—act as danger signals that activate receptors such as TLRs, NLRs, cGAS, and RAGE, triggering signaling cascades that modulate the immune response [1]. The nature of DAMPs, their post-translational modifications, and the timing of their release determine whether the outcome will be immunostimulatory or tolerogenic, making them a central axis for understanding the relationship between cell death and the immune response.

Furthermore, ubiquitination has emerged as a key regulator of apoptotic and necroptotic pathways. This post-translational modification controls the stability and activity of critical proteins, modulating both death receptor signaling and caspase function [8]. Recent evidence demonstrates that ubiquitination not only strictly regulates apoptosis but also influences necroptosis, opening new perspectives on how cells decide between silent death and pro-inflammatory death.

Together, DAMPs and ubiquitination represent fine-tuning mechanisms that determine the immunological impact of MCP. Their study offers opportunities for the development of targeted therapies capable of enhancing immunogenicity in cancer or reducing inflammation in chronic diseases.

3.3. Interconnection of Pathways and PANoptosis

Apoptosis, necroptosis, and pyroptosis, although traditionally described as independent processes, share common molecular components and regulatory points. This interrelation has led to the concept of PANoptosis, understood as the functional convergence of the three forms of MCP [2]. PANoptosis is organized through a multiprotein complex called the PANoptosome, which integrates signals from caspases, RIPK1/RIPK3, and gasdermins, enabling a coordinated response to pathological stimuli.

In the context of cancer, PANoptosis takes on particular significance. It has been shown that this mechanism not only regulates the elimination of tumor cells but also modulates the immune response in the tumor microenvironment. The activation of PANoptosis can influence the function of immune cells such as T lymphocytes and macrophages, affecting tumor progression and patient survival rates [6]. Furthermore, the possibility of manipulating PANoptosis opens up new therapeutic perspectives, as its modulation could enhance antitumor immunity and improve the efficacy of combination therapies.

In summary, PANoptosis represents a central hub integrating apoptosis, necroptosis, and pyroptosis, offering a conceptual framework for understanding how cells choose between different death pathways and how these choices impact cancer pathophysiology and therapy.

3.4. Clinical Implications in Cancer

Necroptosis has emerged as a key mechanism in tumor progression and metastasis. Although it was initially described as a host defense mechanism against infections, its dysregulation has been linked to tumorigenesis and the ability of cancer cells to invade distant tissues [4]. This finding positions necroptosis as a potential therapeutic target in oncology, given that its activation or inhibition can alter the course of the disease.

A particularly relevant aspect is the immunogenic nature of necroptosis. Unlike apoptosis, which is typically immunologically silent, necroptosis releases danger signals capable of activating antigen-presenting cells and promoting the cross-activation of CD8+ T lymphocytes. This process enhances the antitumor immune response and opens the possibility of combining necroptosis-induction strategies with immunotherapy [7].

Taken together, the evidence suggests that necroptosis plays a dual role in cancer: on the one hand, it can promote tumor progression when dysregulated; on the other hand, it can serve as a therapeutic tool by inducing antitumor immunity. This dynamic balance highlights the need to better understand the molecular mechanisms regulating necroptosis in the tumor microenvironment, in order to design more effective and targeted therapies.

3.5. Therapeutic Applications with Pharmacological and Natural Compounds

Evasion of programmed cell death (PCD) is one of the defining characteristics of cancer cells, which has driven the search for therapeutic strategies capable of restoring these pathways. In this context, small-molecule compounds have demonstrated significant potential for modulating apoptosis, necroptosis, and autophagy-dependent cell death. Several studies have identified molecules capable of acting on death receptors, caspases, and autophagy regulators, opening the possibility of designing combination therapies that simultaneously target multiple subroutines of MCR [9].

In addition, natural plant-derived compounds and their derivatives have emerged as promising candidates in cancer therapy. These compounds, extensively studied in pharmacognosy and biomedicine, have demonstrated the ability to induce apoptosis in tumor cells, restore autophagy under conditions of cellular stress, and activate necroptosis in clones resistant to apoptosis [10]. Their advantage lies in their structural and functional diversity, as well as their potentially lower toxicity compared to synthetic agents.

Taken together, both synthetic and natural compounds represent a new generation of therapeutic agents targeting regulated cell death. The possibility of combining them or using them sequentially opens the way to more precise and personalized treatments, capable of overcoming tumor resistance and improving clinical efficacy in patients with advanced cancer.

3.6. Other conditions: diabetic nephropathy

Diabetic nephropathy is one of the most common and serious complications of type 1 and type 2 diabetes mellitus, characterized by progressive glomerular damage, proteinuria, and hypertension. In this context, MCP plays a central role in the pathogenesis. Podocyte apoptosis leads to the loss of these cells, which are essential for the glomerular filtration barrier, resulting in proteinuria and structural damage [7]. Similarly, apoptosis of proximal tubular epithelial cells causes tubular atrophy and the formation of atubular glomeruli, contributing to renal functional decline.

Autophagy, another mechanism regulating cellular homeostasis, is impaired in diabetic nephropathy. Reduced autophagic activity in podocytes and proximal tubular cells promotes the accumulation of damaged organelles and proteins, exacerbating cellular dysfunction and proteinuria [7].

Finally, necroptosis has been identified as an additional process that contributes to kidney damage. Activation of this pathway in podocytes increases inflammation and glomerular dysfunction, suggesting that necroptosis could be a key therapeutic target in preventing the progression of diabetic nephropathy.

Taken together, apoptosis, insufficient autophagy, and necroptosis form a pathogenic triad that accounts for much of the kidney damage in diabetic nephropathy, offering new opportunities for the development of therapies aimed at preserving kidney function in diabetic patients.

4. Conclusion

The evidence gathered demonstrates that the MCP—in its main modalities of apoptosis, necroptosis, pyroptosis, autophagy, and their convergence in PANoptosis—constitutes a central axis in cellular homeostasis and in the pathophysiology of diseases such as cancer and diabetic nephropathy. Understanding its molecular mechanisms, regulatory processes such as ubiquitination, and immunological mediators such as DAMPs, allows us to explain how cells choose between silent and immunogenic death pathways.

In the field of oncology, necroptosis and PANoptosis stand out for their ability to induce antitumor immunity, offering new opportunities to enhance the efficacy of immunotherapy. Furthermore, the identification of small-molecule compounds and natural plant derivatives capable of modulating these pathways paves the way for more precise and personalized therapies capable of overcoming tumor resistance.

In diabetic nephropathy, the combination of apoptosis, necroptosis, and insufficient autophagy accounts for much of the progressive kidney damage, suggesting that manipulating these pathways could become a therapeutic strategy to preserve kidney function.

Taken together, the findings highlight that the targeted modulation of regulated cell death represents not only an expanding field of research but also a promising therapeutic strategy for improving patient survival and quality of life.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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