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The Role of Pyroptosis in the Progression and Targeted Therapeutic Approaches for Urological Malignancies

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Abstract: The prevalence of urological malignancies continues to pose a significant global health challenge, particularly due to the poor prognosis associated with advanced stages of these diseases. Consequently, there is an urgent need to deepen our understanding of the molecular mechanisms governing the development of urological malignancies to facilitate breakthroughs in diagnosis and treatment. Pyroptosis, a novel and specific form of programmed cell death, plays a crucial role in regulating inflammatory responses, cell development, tissue homeostasis, and stress responses. Recent research has revealed a close association between pyroptosis and urological malignancies. In this paper, we review the pathogenesis and recent advancements in the understanding of pyroptosis in urological malignancies, elucidate the molecular mechanisms involved in its regulation, and aim to provide new directions for the clinical management of these diseases.

Keywords: pyroptosis, urological malignancies, mechanism, diagnosis, treatment

Introduction

According to GLOBOCAN 2020, malignancies of the urinary tract constitute approximately 13% of all cancer cases. Among these, prostate cancer (PCa), bladder cancer (BCa), and renal cell carcinoma (RCC) are the most prevalent.[1] PCa is the second most frequently diagnosed malignancy in men and accounts for 6.8% of cancer-related deaths worldwide.[1] BCa ranks as the tenth most commonly diagnosed cancer globally, with urothelial carcinoma being the predominant pathological type, constituting over 90% of BCa cases.[2] RCC, which represents 85% of malignant renal tumors, is characterized by its high morbidity and aggressive malignancy.[3] Despite significant progresses in the diagnosis and treatment of urological malignancies that have markedly improved patient outcomes,[4,5] the mortality rate for individuals with advanced stages of genitourinary cancers remains high.[6,7] This persistent challenge places a considerable burden on public health services and underscores the necessity for ongoing research and innovative therapeutic approaches to better manage these malignancies.[8]

Programmed cell death (PCD) refers to an active, regulated process of cell death that occurs according to a predetermined program.[9] This mechanism is essential for maintaining the stability of the internal environment in response to specific signals or stimuli.[10,11] PCD encompasses various mechanisms, including apoptosis, autophagy, necroptosis, pyroptosis, and ferroptosis. Apoptosis, the first identified and most extensively characterized PCD pathway, plays a critical role in organismal growth, development, and the maintenance of tissue and organ homeostasis. Autophagy, a process prevalent in eukaryotic cells, is intricately regulated by a diverse array of autophagy-related genes (ATGs). Necroptosis represents a gene-regulated, caspase-independent mode of PCD characterized by its reliance on receptor-interacting protein kinases (RIPK). Ferroptosis, in contrast, is an iron-dependent PCD pathway distinguished by the accumulation of lipid peroxidation products within the cellular membrane. Finally, pyroptosis, a recently elucidated PCD pathway, is associated with caspase activation and is implicated in inflammatory responses[12,13] (Table 1). This process is characterized by the formation of pores in the cell membrane, ultimately leading to chromatin

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Table 1 The Morphological Features and Biochemical Pathways of PCDs

PCD	Morphological Features	Biochemical Pathways
Apoptosis	Shrinkaging while maintaining intact cell membranes and exhibiting condensed nucleoplasm, the formation of apoptotic bodies	Degradation of DNA fragments, decrease in mitochondrial membrane potential, activation of caspases
Autophagy	Cell membrane integrity, cytoplasmic vacuolization, autophagosome formation	Production of ATG family proteins, microtubule-associated protein light chain 3 (LC3)-I to LC3-II conversion
Necroptosis	Cell swelling and deformation, loss of cell membrane integrity, formation of necrotic vesicles	RIPK1, RIPK3, MLKL, phosphorylation and ubiquitination of RIPK1, formation of necrosome complexes in cytoplasm
Ferroptosis	Rupture of the cell membrane, decrease in mitochondrial volume, normal nucleus	Iron accumulation, lipid peroxidation
Pyroptosis	Cell membrane rupture, cell swelling	Release of inflammatory factors, caspase activation

fragmentation, cell swelling, and plasma membrane lysis.[14] Initially identified as a vital mechanism for combating infections, pyroptosis has since been increasingly recognized for its role in tumorigenesis and tumor progression.[15] Research has demonstrated that key components of pyroptosis—proinflammatory cytokines, gasdermin proteins, and inflammasomes—are closely associated with invasion, oncogenesis, and metastasis.[16,17] This expanding body of knowledge underscores the critical role of pyroptosis in cancer biology and highlights its potential as a promising therapeutic target.

Growing evidence underscores the importance of understanding the molecular mechanisms underlying urinary malignancies, which could lead to enhanced treatment strategies and improved prognostic outcomes.[18] Insights into these mechanisms are crucial for developing innovative therapeutic approaches for these cancers. Recently, research has increasingly highlighted the significant role of pyroptosis in various cancers, including pediatric cancer,[19] lung cancer,[20] breast cancer,[21] ovarian cancer,[22] anaplastic thyroid cancer[23] and hepatocellular carcinoma.[24] Pyroptosis also plays a critical role in the pathophysiological processes of genitourinary malignancies, attracting considerable attention from urologists and researchers alike.[25] This review aims to summarize current studies on the impact of pyroptosis in urinary system malignancies, shedding light on its potential implications for future research and clinical practice.

Overview of Pyroptosis

In 1992, Zychlinsky et al documented the morphological features of pyroptosis, a form of PCD distinct from apoptosis, induced by Shigella bacteria infection in macrophages. Their findings marked the initial identification of pyroptosis as a caspase-1-mediated cell death process, although the concept was not yet fully established.[26] It was Cookson et al who, in 2001, recognized caspase-1-dependent cell death as a proinflammatory programmed event and coined the term "pyroptosis".[27] In 2005, Fink et al further characterized pyroptosis, describing cells undergoing this process as exhibiting DNA fragmentation, nuclear condensation, swelling, and the release of inflammatory factors.[28] The rupture of pyroptotic cells is mediated by the cleavage of gasdermin D (GSDMD), which produces the N-terminal fragment (GSDMD-N) responsible for cell membrane perforation.[29] This process necessitates the involvement of inflammatory caspases, specifically Caspase-1 and Caspase-4/5/11, with Caspase-11 being the mouse orthologue of human Caspase-4 and −5.[30,31] During pyroptosis, the extracellular release of interleukin-1β (IL-1β) and interleukin-18 (IL-18) provokes robust inflammatory responses.[32] In 2018, the Nomenclature Committee on Cell Death (NCCD) formally defined pyroptosis as a regulated form of cell death caused by the disruption of the plasma membrane by members of the gasdermin protein family, typically triggered by the activation of proinflammatory caspases.[33]

As previously mentioned, members of the gasdermin (GSDM) protein family serve as crucial executioners in the pyroptosis pathway. GSDM proteins are characterized by their distinctive N-terminal domain (NTD) and C-terminal domain (CTD), which are connected by a flexible linker region.[31] In the inactive form of the protein, the CTD inhibits the activity of the NTD. Upon cleavage, the NTD forms protein oligomers that penetrate the plasma membrane, resulting in

pyroptosis and subsequent cell lysis.[34] The initiation of pyroptosis can occur through various caspase-dependent pathways, which are classified into canonical, non-canonical, and other pathways.[35] Each of these pathways represents a distinct mechanism by which pyroptosis can be activated, underscoring the complexity and versatility of this form of programmed cell death.[15,36]

Canonical Pyroptotic Pathway

Canonical pyroptosis is a caspase-1-mediated process that involves inflammasome assembly, gasdermin D (GSDMD) cleavage, and the release of interleukins, predominantly IL-1β and IL-18.[37] Typical inflammasomes are composed of pattern recognition receptors (PRRs), adapter proteins (ASC), and inactive pro-caspase-1 proteins. PRRs are expressed on various immune cells and are crucial for detecting molecular patterns associated with tissue damage or pathogen infection.[38] These receptors detect intracellular and extracellular signals, primarily danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). This recognition triggers a cascade of signaling events that culminate in the release of pro-inflammatory cytokines and GSDMD-mediated cell death.[39]

Pyroptosis is associated with various PRRs, including Toll-like receptors (TLRs), absent in melanoma 2 (AIM2)-like receptors (ALRs), and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs).[40] PRRs can detect hazard signals from a variety of sources, such as fungi, viruses, bacteria, bacterial toxins, nucleic acids, parasites, certain drugs, reactive oxygen species (ROS), silica, crystalline materials, and endogenous markers of tissue damage.[41] The canonical inflammasome can be assembled by inflammasome sensors, which include Nodal receptor protein 1 (NLRP1), NLRP3, NLR family CARD domain-containing protein 4 (NLRC4), AIM2, and Pyrin.[42] These sensors detect various microbial or intracellular danger signals and activate caspase-1.[43] Upon activation, caspase-1 cleaves intact GSDMD into two domains: the N-terminal structural domain (GSDMD-N) and the C-terminal structural domain (GSDMD-C). GSDMD-N subsequently integrates into the cell membrane, forming large oligomerization pores that disrupt ion homeostasis and induce cellular pyroptosis.[44] Furthermore, caspase-1 stimulates the production of IL-1β and IL-18, thereby enhancing cellular pyroptosis[45] (Figure 1).

Noncanonical Pyroptotic Pathway

Unlike the classical inflammasome pathway, the atypical inflammasome pathway involves direct activation of caspase-11 in mouse cells or caspase-4/5 in human cells by lipopolysaccharide (LPS).[46] This activation results in the cleavage of GSDMD, forming GSDMD-N pores that facilitate the exocytosis of K+ ions, which subsequently leads to the maturation and release of IL-1β and IL-18.[47]

Additionally, it has been demonstrated that caspase-11 can induce the cleavage of pannexin-1 channels and the release of ATP in response to LPS stimulation. This release of ATP activates the ATP-gated ion channel P2X7, ultimately leading to the activation of the NLRP3 inflammasome and caspase-1[48] (Figure 1).

New Mechanisms in Pathways of Pyroptosis

Caspase 3/8 Mediated Pathway

It has been observed that chemotherapeutic agents mediate the cleavage of GSDME through the activation of caspase-3, leading to the formation of N-GSDME, which, in turn, activates inflammasomes and initiates the classical pyroptotic pathway, ultimately inducing pyroptosis.[49,50]

In mouse macrophages, inhibition of TGF-β-activated kinase 1 (TAK1) has been shown to induce caspase-8-mediated cleavage of GSDMD, leading to pyroptosis.[51,52] Conversely, under hypoxic conditions, phosphorylated Stat3 facilitates the nuclear translocation of PD-L1, which enhances the transcription of GSDMC. At this stage, caspase-8 specifically cleaves GSDMC in response to TNF-α stimulation, generating N-GSDMC and subsequently inducing pyroptosis[53] (Figure 1).

Granzymes Mediated Pathway

Granzymes are serine proteases stored in the cytoplasmic granules of cytotoxic lymphocytes and natural killer cells. Notably, lymphocyte-derived granzyme A (GzmA) can directly cleave GSDMB, resulting in the formation of N-GSDMB

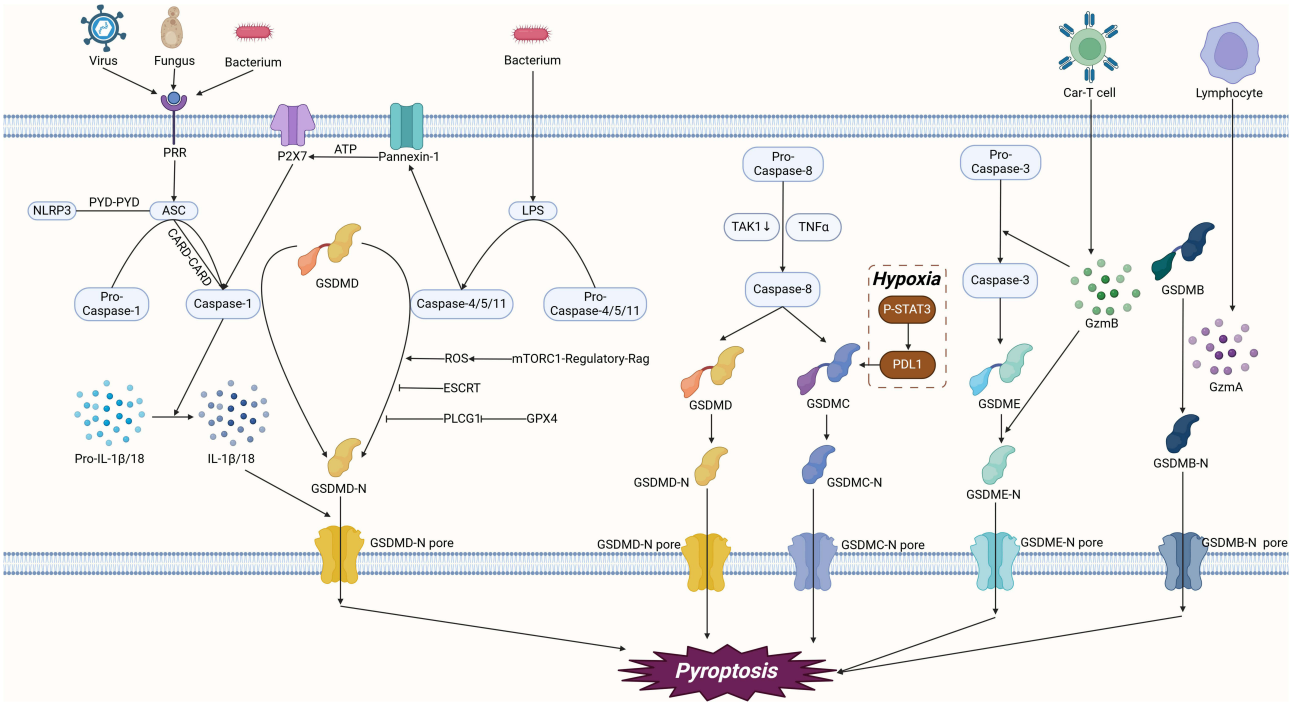

Figure 1 Pathways of pyroptosis. In the canonical pyroptotic pathway, PRRs detect various inflammatory signals and activate caspase-1 through the adaptor protein ASC. Activated caspase-1 then cleaves GSDMD into its GSDMD-N, which forms pores in the cell membrane, leading to cell death. Caspase-1 also stimulates the production of interleukins IL-1β and IL-18, further promoting cell death. In the noncanonical pyroptotic pathway, LPS can directly activate caspase-4, caspase-5, and caspase-11. These caspases similarly cleave GSDMD into GSDMD-N, inducing pyroptosis. Additionally, it has been observed that NLRP3 can activate caspase-1 through its structural domains, and the cleavage of GSDMD into GSDMD-N can be regulated by multiple signaling pathways, highlighting the complexity and regulation of the pyroptotic process. Additionally, pyroptosis can be activated via the caspase-3/8 pathway or the granzyme pathway (Created in BioRender. Li, Y. (2024) https://BioRender.com/f83v842).
Abbreviations: PPRs, pattern recognition receptors; ASC, adapter proteins; GSDMD, gasdermin D; NLRP3, nodal receptor protein 3; LPS, lipopolysaccharide; ESCRT, endosomal sorting complexes required for transport; GPX4, glutathione peroxidase 4; PLCG1, phospholipase C gamma 1; ROS, reactive oxygen species.

pores in the cell membrane, thereby inducing pyroptosis.[54] In contrast, chimeric antigen receptor (CAR) T cell-derived GzmB can induce pyroptosis both through the activation of caspase-3 and via direct cleavage of GSDME[55,56] (Figure 1).

The Regulation of NLRP3

The NLRP3 receptor protein is composed of three structural domains: PYD, NACHT, and LRR. The PYD of NLRP3 can interact with the PYD of the adaptor protein ASC through a homotypic PYD-PYD interaction.[15,45] Additionally, the CARD in ASC can bind to the CARD of caspase-1, forming a CARD-CARD interaction. This interaction promotes the maturation of caspase-1 and the cleavage of GSDMD, which ultimately results in the secretion of inflammatory factors and the initiation of pyroptosis[57] (Figure 1).

The Regulation of GSDMD

As previously mentioned, GSDMD can be cleaved to form GSDMD-N, which subsequently creates pores in the cell membrane. Recent studies have identified several factors that influence the formation of these cell membrane pores following GSDMD cleavage. For instance, the mTORC1-Regulatory-Rag pathway has been shown to regulate the formation of GSDMD-N-induced membrane pores by promoting the production of ROS.[58] Ruhl et al demonstrated that the endosomal sorting complexes required for transport (ESCRT) system could repair the cell membrane pores formed by GSDMD without impeding its activation, thereby inhibiting the release of IL-1β and the occurrence of pyroptosis.[59] Additionally, glutathione peroxidase 4 (GPX4) was found to inhibit the formation of phospholipase C gamma 1 (PLCG1) by preventing lipid peroxidation, which in turn suppresses the production of GSDMD-N[60] (Figure 1).

The Mechanisms and Potential Therapeutic Applications of Pyroptosis in Urological Malignancies

The Mechanisms and Potential Therapeutic Applications of Pyroptosis in PCa

PCa is the most frequently diagnosed cancer among men in over half of the world's countries (112 out of 185) and ranks as the fifth leading cause of cancer-related death in men. In 2020, approximately 1.4 million new cases and 375,000 deaths were reported globally.[1] Recent years have seen extensive research providing evidence that various drugs capable of inducing pyroptosis in PCa cells, thereby triggering pyroptosis, can effectively suppress tumor progression (Figure 2, Table 2).

Luo et al in their evaluation of risk models through the establishment of six scotoma-associated genes, identified that ZDHHC1 can promote scotoma by activating caspase-1 and caspase-2. This discovery provides a new perspective for studying the clinical applications of scotoma in PCa.[77] Separately, Zhang et al have pinpointed gambogic acid (GBA) as a specific inducer of pyroptosis in PCa cells. Employing a thermal proteome profiling (TPP) strategy, they demonstrated that GBA induces pyroptosis by directly targeting the canopy FGF signaling regulator (CNPY3). Moreover, using the APEX2-based proximity labeling method, they revealed that GBA recruits deacetylase SIRT1, facilitating the removal of lysine lactylation (Kla) from CNPY3. Notably, SIRT1-mediated delactylation alters CNPY3's cellular localization, prompting lysosomal rupture and triggering pyroptosis. Consequently, lysosomal rupture and activation of Cathepsin B (CatB) primarily induce pyroptosis via the caspase-1/GSDMD pathway. Overall, this study identifies CNPY3 as a distinctive cellular target for inducing pyroptosis and underscores its potential therapeutic application in PCa.[61] Zhang et al elucidated the anticancer properties of a newly synthesized 3',5'-dienylated chalcone (C10), which induced both caspase-mediated apoptosis and GSDME-dependent pyroptotic events. Mechanistic studies revealed that C10 treatment activated the PKCδ/JNK signaling pathway, subsequently activating caspase-3. This activation resulted in the cleavage of PARP and GSDME, leading to both apoptosis and pyroptosis in PCa cells. These findings highlight the potential of C10 as a therapeutic agent that simultaneously triggers dual cell death pathways to combat PCa.[62] Analysis by Zeng et al revealed a reduction in the expression levels of NLRP3, caspase-1, ASC, and GSDMD in PCa tissues compared to normal tissues, without any prognostic significance. Additionally, their study revealed that CVL promotes NF-κB nuclear translocation and upregulates NLRP3 inflammasome expression, ultimately inducing pyroptosis in PCa cells through the NLRP3-caspase-1-ASC inflammasome pathway. As

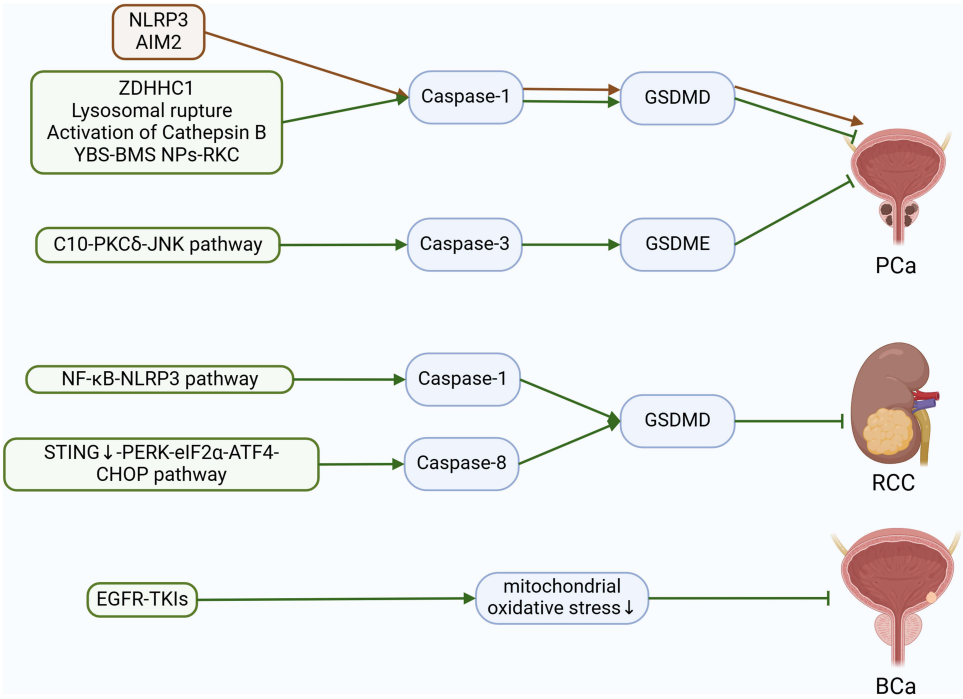

Figure 2 The mechanisms and potential therapeutic applications of pyroptosis in urological malignancies (Created in BioRender. Li, Y. (2024) https://BioRender.com/j91x069).
Abbreviations: GSDMD, gasdermin D; NLRP3, nodal receptor protein 3; AIM2, absent in melanoma 2.

Table 2 The Mechanisms and Potential Therapeutic Applications of Pyroptosis in Urological Malignancies

Cancers	Drug	Target	Pyroptosis (Inducer Inhibitor)	Target (Mechanism)	Biological Function	Model	Reference
PCa		ZDHHC1	Inducer	Activate caspase-1 and caspase-2	Higher probability of biochemical recurrence (BCR), higher immune infiltration, and worsened clinicopathological features.	In vitro	[61]
	Gambogic acid	CNPY3	Inducer	Promote lysosome rupture, activate caspase-1		In vitro	[62]
	A novel 3',5'-diprenylated chalcone (C10)		Inducer	Induce the PKCδ/JNK pathway, thereby activating Caspase-3 and GSDME to execute pyroptosis	Execute apoptosis and cell-lytic pyroptosis in prostate cancer cells	In vitro and in vivo	[63]
	Carvedilol (CVL)		Inducer	Promote nuclear translocation of NF-κB through NLRP3-caspase1-ASC inflammasome	Inhibit tumor growth	In vitro and in vivo	[64]
		NLRP3	Inducer	Activate NLRP3/caspase-1 inflammasome	Promote the malignant progression of PCa	In vitro and in vivo	[65]
		AIM2	Inducer	IFNs (α, β, or γ) induce AIM2 expression	Cytosolic DNA activates the AIM2 inflammasome	In vitro and in vivo	[66]
	YBS-BMS NPs-RKC		Inducer		Stimulate a powerful antitumor immune response to suppress primary tumor progression and evoke long-term immune memory to inhibit tumor relapse and metastasis	In vitro and in vivo	[67]
	Olaparib		Inducer	Caspase-3 cleavage of GSDME		In vitro and in vivo	[68]
RCC		CASP4 and CASP8	Inducer		Higher pathological staging and poorer prognosis		[69]
		Stimulator-of-interferon genes (STING)	Inhibitor	Activate of the PERK/eIF2α/ATF4/CHOP pathway and cleavage of Caspase-8, thereby inducing GSDMD-mediated pyroptosis	Poorer overall survival rates	In vitro and in vivo	[70]
	JQ1	BRD4	Inducer	Activate the NF-κB–NLRP3–caspase-1 pyroptosis signaling pathway	Prevent cell proliferation and epithelial-mesenchymal transition progression	In vitro and in vivo	[71]
		AIM2	Inducer	AIM2-inflammasome-caspase1	Promote tumor progression		[72,73]
		linc00023	Inducer	Inhibit p53		In vitro and in vivo	[74]
BCa	AG1478		Inducer	Induce mitochondrial oxidative stress damage		In vitro	[75]
	MNCICGNIG@SiO2		Inducer	ICG-mediated generation of reactive oxygen species, Se—Se bond cleavage, and subsequent NIG release	Optimize and enhance the efficacy of BCG immunotherapy by precisely modulating the cytokines	In vitro and in vivo	[76]

previously mentioned, the NLRP3 inflammasome is a cytoplasmic multiprotein complex composed of the innate immune receptor proteins NLRP3, ASC, and caspase-1. Upon activation of caspase-1 in response to microbial infections, endogenous danger signals, or environmental stimuli, the inflammasome promotes the release of IL-1β and IL-18 and triggers GSDMD-dependent pyroptosis, thereby enhancing innate immune defenses. These findings suggest the potential therapeutic use of adrenergic receptor antagonists in prostate cancer treatment.[63] Similarly, Xu's study demonstrated that, in addition to comparable findings, knockdown of NLRP3 inhibited tumor growth in PCa. The study further revealed that the NLRP3

inflammasome plays a significant role in promoting PCa malignancy through caspase-1 activation.[64] In clinical tumor specimens, AIM2 mRNA levels were significantly reduced. As an inflammasome sensor, AIM2 may also play a role in PCa progression by functioning as an inflammasome component.[65]

PCa is classified as an immunogenic "cold" tumor, and its response to immunotherapy has been largely unsatisfactory in clinical practice.[66] Pyroptosis exhibits promising potential by activating the antitumor immune response, enhancing cytotoxic T-lymphocyte infiltration, and converting tumors from "cold" to "hot". Despite these advantageous attributes, the clinical utility of pyroptosis-inducing drugs remains significantly restricted, primarily due to the upregulation of tumor PD-L1, which amplifies immune evasion post-photo-immunotherapy. Addressing these challenges, Wang et al innovatively devised a pH-responsive nano-photosensitizer (YBS-BMS NPs-RKC) integrating immunogenic pyroptosis induction with immune checkpoint blockade. Facilitated by pH-responsive polymeric micelles (LSPM), RKC peptides precisely target the tumor microenvironment (TME), effectively anchoring the nano-photosensitizer to cell membranes. This targeted approach triggers localized ROS generation on the cell membrane, thereby activating the caspase-1/GSDMD pathway and inducing immunogenic pyroptosis. This study introduces a synergistic platform for PCa immunotherapy and proposes a novel avenue for developing biocompatible, photo-controlled pyroptosis inducers, potentially revolutionizing therapeutic strategies for PCa.[78]

Pyroptosis is also able to synergize with current clinical medications. Tian et al discovered a significant reduction in the expression level of GSDME in PCa. They observed that the reduced expression of GSDME was inversely correlated with its methylation level in PCa tissues. Subsequent experiments demonstrated that olaparib could induce pyroptosis by cleaving GSDME through the activation of caspase-3. Moreover, the overexpression of GSDME amplified the pyroptotic response. Additionally, the use of the DNA methyltransferase inhibitor decitabine reversed the epigenetic silencing of GSDME, thereby enhancing the antitumor efficacy of olaparib synergistically.[67]

The Mechanisms and Potential Therapeutic Applications of Pyroptosis in RCC

According to GLOBOCAN 2020, RCC ranks as the 14th most common cancer worldwide, with over 400,000 new cases and more than 170,000 deaths reported in 2020. Clear cell renal cell carcinoma (ccRCC) is the predominant histologic subtype, comprising approximately 80% of RCC cases.[1] Pyroptosis can influence the progression of RCC through diverse mechanisms that ultimately impact pyroptosis-related genes (PRGs) or long non-coding RNAs (lncRNAs). Consequently, exploring therapeutic approaches for RCC that leverage pyroptosis represents a promising new avenue for research and potential clinical applications (Figure 2, Table 2).

Li et al discovered that CASP4 and CASP8, genes associated with autophagy and pyroptosis, were significantly upregulated in RCC tumor tissues. The elevated expression of CASP4 and CASP8 correlated with advanced pathological stages and poorer prognoses. Prognostic charts based on CASP4 and CASP8 expression levels more accurately predicted the survival rates of RCC patients. Additionally, the increased expression of CASP4 and CASP8 showed a strong correlation with the levels of various infiltrating immune cell types.[68] Wu et al unveiled that RCC displays an aberrant reliance on the stimulator of interferon genes (STING) for survival and evades immune surveillance by thwarting endoplasmic reticulum stress-mediated pyroptosis. Their findings underscored a substantial amplification and upregulation of STING in RCC, correlating with adverse clinical outcomes. Mechanistically, STING deletion in RCC cells specifically triggered activation of the PERK/eIF2α/ATF4/CHOP pathway, culminating in Caspase-8 activation and subsequent induction of GSDMD-mediated pyroptosis, independent of STING's conventional innate immune pathway. Moreover, animal studies showcased that STING depletion bolstered infiltration of CD4+ and CD8+ T cells, thereby amplifying anti-tumor immunity through inflammation instigated by pyroptosis. From a targeted therapeutic perspective, the study identified compound SP23, a PROTAC STING-degrading agent, to exhibit comparable efficacy to STING depletion in treating RCC both in vitro and in vivo. Thus, pharmacological degradation of STING by SP23 emerges as a promising strategy for advanced RCC treatment, offering a novel avenue to potentiate immune-mediated tumor eradication.[69] Tan et al demonstrated that BRD4, an epigenetic reader belonging to the bromodomain and extra terminal domain (BET) family, exhibits significant upregulation in RCC, while pyroptosis-related proteins are notably diminished. Inhibiting BRD4, either through gene knockdown or utilizing the inhibitor JQ1, suppressed RCC cell proliferation and inhibited epithelial-mesenchymal transition (EMT) progression, concurrently inducing caspase-1-dependent pyroptosis both in vitro and in vivo. Mechanistically, the antitumor effects of

BRD4 inhibition in RCC were mediated via activation of the NF-κB/NLRP3/caspase-1 pyroptosis signaling pathway. The NLRP3 inflammasome influences cancer pathogenesis by regulating immune responses, cell proliferation, and cell death. Furthermore, NLRP3 levels were found to be low in RCC tumor samples, suggesting a potential role as a tumor suppressor in RCC. When NLRP3 expression was inhibited, the BRD4 inhibition-driven promotion of pyroptosis and suppression of proliferation were attenuated. Thus, BRD4 inhibition exerts anticancer effects by inducing NLRP3 inflammasome activation and subsequent pyroptosis, and the BRD4 inhibitor JQ1 is a promising therapeutic candidate for RCC.[70] In addition to NLRP3 inflammasomes, analysis of The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) databases revealed that AIM2 inflammasomes were upregulated in ccRCC. This upregulation was associated with the activation of immune pathways, suggesting a potential role for AIM2 in promoting tumor progression.[71,72] The lncRNA Linc00023 expression was found to be significantly downregulated in RCC cells. Knockdown of linc00023 led to an increase in cell proliferation and a reduction in cellular pyroptosis. Additionally, the inhibition of linc00023 altered the expression of various mRNAs, notably including p53. The introduction of ReACp53, a p53-activating factor, counteracted the effects of linc00023 knockdown on both cell proliferation and pyroptosis. Consequently, linc00023 facilitates pyroptosis through the regulation of p53 expression in RCC.[73]

The Mechanisms and Potential Therapeutic Applications of Pyroptosis in BCa

BCa ranks as the tenth most common cancer worldwide, with approximately 573,000 new cases and 213,000 deaths reported in 2020. Bladder cancer occurs about four times more frequently in men than in women and is the sixth most common cancer and ninth leading cause of cancer-related mortality among men.[1] Most patients require long-term cystoscopic surveillance and repeated therapeutic interventions, leading to a substantial healthcare burden. Consequently, BCa is considered the most costly malignancy to treat.[74] In BCa, pyroptosis has been employed not only in understanding drug treatment mechanisms that have already been applied clinically but also in studying the preparation of engineered nanoparticles. These applications offer innovative approaches and provide new insights for the treatment of BCa (Figure 2, Table 2).

Yu et al conducted an intervention study on the BCa cell line T24 using the epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) AG1478. The results demonstrated that EGFR-TKI treatment significantly decreased cell viability, enhanced apoptosis, and arrested cells predominantly in the G0/G1 phase, underscoring the potential of EGFR-TKIs in BCa therapy. Furthermore, the researchers observed that AG1478 also induced pyroptosis in T24 cells, a process linked to mitochondrial oxidative stress damage. These findings provide a robust foundation for the therapeutic application of EGFR-TKIs in BCa.[79]

Engineered macrophages hold significant promise for drug delivery and immunotherapy in cancer treatment.[75,80] In BCa, macrophages were modified to induce cellular pyroptosis. These engineered macrophages utilized selenium-selenium (Se─Se) bond-modified SiO_2 nanoparticles, which were loaded with advanced nanoparticles containing indocyanine green (ICG) and Nigerian mycobactin (NIG), referred to as MNCICGNIG@SiO2 (MINS). These nanoparticles were further encapsulated with CpG-conjugated magnetic nanoclusters (MNCs) and applied surgically, followed by Bacillus Calmette-Guérin (BCG) adjuvant therapy. Upon intravenous administration, the local inflammation induced by BCG within the tumor resulted in the targeted accumulation of MINS@MΦ. Within the tumor tissue, these macrophages were immunologically activated by laser irradiation, which led to the production of ROS mediated by ICG. This ROS production caused the breaking of Se─Se bonds and the subsequent release of NIG, thereby inducing pyroptosis. This innovative approach significantly enhances the efficacy of BCG therapy by precisely modulating cytokine activity, offering an effective strategy for treating BCa.[81]

Predictive Markers of Urological Malignancies Associated with Pyroptosis

Predictive Markers of PCa Associated with Pyroptosis

With the rise in prostate-specific antigen (PSA) screening, an increasing number of patients are undergoing radical local therapy. However, despite these advancements, 30% to 40% of PCa patients still experience biochemical recurrence or metastasis following treatment.[76,82] Although several prognostic indicators have been established for

PCa, they exhibit limitations in accurately forecasting the timing of biochemical recurrence.[83] Consequently, developing a biomarker with high accuracy and specificity is essential for improving prognosis prediction and guiding the treatment of PCa.[84]

Luo et al developed a risk model based on six PRGs and validated its predictive ability for prognosis and treatment outcomes. To ensure the reliability of their findings, they first evaluated the model using TCGA dataset, followed by validation in the GEO cohort. Their results provided a robust and scientifically reliable prediction of biochemical recurrence in PCa patients, offering new insights for further research on focal death and its clinical applications in PCa.[77] Similarly, the study conducted by Hu et al revealed that the expression levels of most PRGs varied significantly not only between normal and tumor tissues but also among different cell clusters. By classifying these distinct clusters and utilizing PRGs as a focal point, their research integrated expression profiles with clinical data to construct a prognostic signature with high predictive value for biochemical recurrence following radical prostatectomy (RP). Moreover, the study delved into the relationships between pyroptosis, the immune microenvironment, and PCa, providing critical insights and valuable clues for future research on focal death and immune interactions in PCa.[85] Fu et al identified two modes of scotomization by analyzing predicted scotomization genes at both the bulk RNA-seq and single-cell levels. They screened for differentially expressed genes (DEGs) between these categories and developed a novel prognostic genetic marker. This signature was subsequently validated using two external databases, demonstrating its efficacy as an independent factor associated with recurrence-free survival in PCa patients.[86]

Predictive Markers of RCC Associated with Pyroptosis

RCC is one of the deadliest malignancies, often diagnosed at an advanced stage, with approximately 33% of cases already metastatic at the time of diagnosis, leading to limited and less effective treatment options.[87,88] Potential predictive markers for RCC encompass various types, including toxicity-based, serum, radiologic biomarkers et al.[89] The primary aim of developing these predictive biomarkers is to enable rational and personalized treatment strategies, thereby providing accurate prognostic predictions for patients with RCC.

Ma et al identified two distinct molecular isoforms through clustering of PRGs. Cluster 1, termed the angiogenic subtype, is distinguished by the activation of classical oncogenic pathways, particularly the angiogenic pathway. In contrast, Cluster 2, known as the inflammatory subtype, is characterized by the activation of immune-related pathways, elevated levels of immunosuppressive cells, depleted CD8+ T cells, and infiltration of tumor-associated fibroblasts. These two subtypes hold prognostic significance in predicting the response of ccRCC to specific therapies. Patients classified under Cluster 1 demonstrated substantial benefit from anti-angiogenic therapy, while those categorized under Cluster 2 exhibited more favorable responses to anti-PD1 inhibitor therapy. This classification offers a refined approach to tailoring treatment strategies for ccRCC patients, thereby augmenting therapeutic efficacy based on the molecular characteristics of their tumors.[90] A study by Khan et al revealed that elevated levels of pyroptosis are linked to a poorer prognosis in RCC, including overall survival, progression-free survival, and disease-specific survival, as determined by Kaplan-Meier survival curves. Additionally, the level of pyroptosis strongly indicates a more active tumor immune microenvironment, characterized by a higher presence of CD8+ T cells and other T cell subtypes. The study also noted that alterations in PRGs significantly affect pyroptosis levels and cancer prognosis. While a relatively hot tumor immune microenvironment was associated with pyroptosis, it did not correlate with cancer prognosis.[91] PANoptosis is a cell death pathway that integrates the mechanisms of pyroptosis, apoptosis, and necroptosis, and is closely linked to cancer immunity and progression.[92] The study by Jiang et al developed a risk model based on PANoptosis, which accurately predicts the prognosis of patients with RCC. This model's correlation with the tumor immune microenvironment and drug efficacy offers promising therapeutic targets and has the potential to significantly influence clinical decision-making.[93] Necroptosis and pyroptosis, recently identified forms of immunogenic cell death within the TME, play a crucial role in tumor metastasis.[94] Fu et al conducted a comprehensive analysis of the transcriptional variants and expression patterns of necroptosis- and pyroptosis-related genes (NPRGs). Through the identification of necroptosis-pyroptosis clusters and employing GSVA enrichment analysis, they explored the potential functional annotations of these clusters. Utilizing the NPRGs score, they constructed and validated prognostic models. Patients with high NPRGs scores exhibited significant differences in clinical features, malignant tumor growth,

recurrence (CSC index), TME cell infiltration, and immunotherapeutic response compared to those with low NPRGs scores. These findings indicate that NPRGs scores could have multifunctional applications in clinical therapy settings. Additionally, AIM2, CASP4, GSDMB, NOD2, and RBCK1 were highly expressed in RCC cell lines and tumor tissues, with CASP4 and GSDMB promoting RCC cell proliferation, migration, and invasion. This study suggests that characterizing the TME based on NPRGs score features may offer valuable insights for its clinical application in predicting the prognosis of RCC.[95]

In addition to PRGs, lncRNAs have emerged as potential biomarkers for renal diseases, often exhibiting significant correlations with pyroptosis in these conditions.[96] Utilizing TCGA database and Sankey plots, Liu et al first identified pyroptosis-associated lncRNAs in RCC patients. Subsequently, they developed and validated the model PLnRM specifically for RCC patients. The grouping capability of PLnRM was confirmed through principal component analysis. They employed PLnRM to evaluate the tumor immune microenvironment and the response to immunotherapy. Furthermore, they analyzed the immunological and molecular characteristics of different PLnRM subgroups, along with clinical features of RCC patients and their predictive risk profiles. Based on these analyses, predictive maps were constructed and evaluated, leading to the identification of new candidate compounds for PLnRM. This comprehensive approach underscores the potential of PLnRM in enhancing prognostic accuracy and guiding therapeutic strategies for RCC patients.[97]

Predictive Markers of BCa Associated with Pyroptosis

Pyroptosis exerts profound effects on tumor cell proliferation, invasion, and metastasis, holding significant clinical importance across various tumor types. Despite these implications, the role of focal death in the progression and prognosis of BCa remains inadequately understood.

Deng et al directed a study that established the focal death risk score as an independent prognostic predictor for BCa. The study found that activity in multiple steps of the anticancer immune response cycle was significantly elevated in the high-risk score group compared to the low-risk score group. Furthermore, BCa with a high pyroptosis risk score was associated with an inflammatory phenotype. The expression of several immune checkpoints was positively correlated with the immunotherapeutic response, and the enrichment score of gene features was positively associated with the pyroptosis risk score. Consequently, patients with high pyroptosis risk scores may exhibit increased sensitivity to immunotherapy. Additionally, patients with elevated pyroptosis risk scores might respond better to chemotherapeutic agents. The pyroptosis risk score also accurately predicted the molecular subtype of BCa and was validated across multiple independent systems.[98]

In Du et al's research, based on the TCGA database, 33 PRGs were assessed for somatic mutations, copy number variations, correlations, and expression levels. Consistent clustering categorized BCa cases into two distinct groups, revealing that genes associated with pyroptosis were significantly correlated with overall survival in BCa patients. Using LASSO Cox regression, a prognostic model incorporating seven PRGs was constructed. Survival analysis curves and receiver operating characteristic curves demonstrated the model's ability to predict the prognosis of BCa patients. Furthermore, univariate and multivariate Cox regression analyses confirmed the model's independent prognostic value. Immune infiltration analysis revealed notable differences in the infiltration of six types of immune cells, with immunotherapy proving to be more effective in the low-risk group.[99] Based on transcriptomic data, Zhang et al developed a novel prognostic model known as the PRGs Score (PRGScore). This model encapsulated immunological features, genomic alterations, and clinical characteristics linked to the pyroptosis phenotype. Samples with elevated PRGScore demonstrated enhanced CD8+ T-cell effector functions, improved antigen processing mechanisms, and upregulated immune checkpoints, indicating a superior immunotherapeutic response to PD-1 and PD-L1 inhibitors. These findings suggested that PRGScore was a valuable marker for identifying patient populations that were particularly sensitive to immune checkpoint inhibitors.[100]

The study conducted by Lu et al sought to develop a prognostic characterization of BCa based on thermophagy-associated lncRNAs. Utilizing the TCGA database, they identified differentially expressed thermophagy-associated lncRNAs in BCa. Through multivariate Cox regression analysis, four lncRNAs—AL121652.1, AL161729.4, AC007128.1, and AC124312.3—were identified, and a prognostic risk model was constructed. Patients were categorized

into low-risk and high-risk groups based on the median risk score. Kaplan-Meier survival analysis indicated that the overall survival rate of BCa patients in the low-risk group was significantly higher than that of patients in the high-risk group. The reliability of the model was further confirmed by receiver operating characteristic curves. Additionally, gene set enrichment analysis (GSEA) revealed significant enrichment of different signaling pathways between the two groups. Analyses of immune infiltration, immune checkpoints, and N6-methyladenosine-related genes also highlighted significant differences between the two groups. Therefore, this prognostic risk model, based on thermophagy-associated lncRNA levels, enables individualized assessment of patient risk and informs clinical treatment decisions. It also contributes to a deeper understanding of the prognosis and treatment strategies for BCa.[101] Similarly, the study conducted by Lu et al demonstrated a close association between pyroptosis and BCa. The researchers generated risk scores based on the expression of 12 pyroptosis-associated lncRNAs and evaluated these scores against various clinical characteristics. These characteristics included survival status, TME, clinicopathological features, and response to chemotherapy. The findings from this study may serve as an important foundation for future research on the role of pyroptosis in BCa, potentially leading to novel prognostic tools and therapeutic strategies.[102]

Research has confirmed that cytotoxic lymphocytes rely on pyroptosis to eliminate tumor cells, indicating that pyroptosis plays a pivotal role in the immune response.[54,103] Chen et al revealed a significant correlation between the imbalance in the expression of focal death-related molecules and genomic variants in BCa. This suggested that pyroptosis was crucial in shaping the TME. Assessing the pattern of pyroptosis alterations could enhance our understanding of TME infiltration and inform the development of more effective immunotherapy strategies.[104]

Discussion and Prospects

In recent years, pyroptosis, a novel and unique form of PCD, has garnered significant attention for its potential applications in anticancer therapy. However, research findings on the relationship between pyroptosis and tumor behavior remain somewhat inconsistent, as pyroptosis appears to have a dual role in tumors. On one hand, pyroptosis can inhibit tumor cell proliferation by triggering acute inflammation and enhancing immune responses. On the other hand, pyroptosis-induced chronic necrosis of a small number of tumor cells in the hypoxic tumor core may weaken anti-tumor immunity, potentially creating a nutrient-rich microenvironment conducive to cancer cell growth and thus promoting tumor proliferation. This duality may result from tumor heterogeneity and the complexity of the tumor microenvironment.

From a tumor-specific perspective, research on urological tumors, particularly PCa, has investigated the mechanisms and potential of pyroptosis. Notably, pyroptosis may convert prostate cancer from a “cold tumor” to a “hot tumor”, presenting new opportunities to counter immune escape following immunotherapy. Additionally, pyroptosis can be used synergistically with other therapeutic agents to enhance the efficacy of current clinical treatments. Studies have already explored the combination of cellular pyroptosis with engineered macrophages, opening new avenues for integrating pyroptosis with precision and targeted therapies against tumors.[81]

Nonetheless, current research on pyroptosis has limitations. First, the dual role of pyroptosis in both promoting and inhibiting tumorigenesis and progression, along with its intricate relationship with related inflammasomes, requires further exploration. Deeper investigation into its signaling pathways, regulatory mechanisms, and pathological significance could yield new approaches to cancer prevention and treatment. Additionally, as a form of programmed cell death, the relationship between pyroptosis and other PCD modalities remains unclear. Clinically, the interplay between pyroptosis and treatments such as radiotherapy and immunotherapy has yet to be fully elucidated, and there is a shortage of relevant clinical trials. Its utility as a predictive marker also requires further clinical validation. In conclusion, optimizing the regulation of tumor cell death to achieve effective therapeutic outcomes remains an area for ongoing exploration.

Conclusion

Pyroptosis significantly influences urological malignancies by contributing to tumor initiation, progression, and response to therapy. Elucidating the molecular mechanisms underpinning pyroptosis in PCa, RCC and BCa could pave the way for developing innovative, targeted therapeutic strategies. Enhancing anti-tumor immune responses and modulating

pyroptosis-related pathways offer promising avenues for improving clinical outcomes in urological malignancies. Further research is imperative to comprehensively understand and harness the potential of pyroptosis as a therapeutic target in these cancers.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Jubber I, Ong S, Bukavina L, et al. Epidemiology of bladder cancer in 2023: a systematic review of risk factors. *Eur Urol*. 2023;84(2):176–190. doi:10.1016/j.eururo.2023.03.029
3. Rini BI, Campbell SC, Escudier B. Renal cell carcinoma. *Lancet*. 2009;373(9669):1119–1132. doi:10.1016/S0140-6736(09)60229-4
4. Lopez-Beltran A, Cookson MS, Guercio BJ, Cheng L. Advances in diagnosis and treatment of bladder cancer. *BMJ*. 2024;384:e076743. doi:10.1136/bmj-2023-076743
5. Al Hussein Al Awamlh B, Wallis CJD, Penson DF, et al. Functional outcomes after localized prostate cancer treatment. *JAMA*. 2024;331(4):302–317. doi:10.1001/jama.2023.26491
6. Li F, Zheng Z, Chen W, et al. Regulation of cisplatin resistance in bladder cancer by epigenetic mechanisms. *Drug Resistance Updates*. 2023;68:100938. doi:10.1016/j.drup.2023.100938
7. Tan SK, Hougen HY, Merchan JR, Gonzalgo ML, Welford SM. Fatty acid metabolism reprogramming in ccRCC: mechanisms and potential targets. *Nat Rev Urol*. 2023;20(1):48–60. doi:10.1038/s41585-022-00654-6
8. Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet*. 2018;392(10159):2052–2090. doi:10.1016/S0140-6736(18)31694-5
9. Tower J. Programmed cell death in aging. *Ageing Res Rev*. 2015;23(Pt A):90–100. doi:10.1016/j.arr.2015.04.002
10. Bedoui S, Herold MJ, Strasser A. Emerging connectivity of programmed cell death pathways and its physiological implications. *Nat Rev Mol Cell Biol*. 2020;21(11):678–695. doi:10.1038/s41580-020-0270-8
11. Camilli G, Blagojevic M, Naglik JR, Richardson JP. Programmed cell death: central player in fungal infections. *Trends Cell Biol*. 2021;31(3):179–196. doi:10.1016/j.tcb.2020.11.005
12. Yuan J, Ofengeim D. A guide to cell death pathways. *Nat Rev Mol Cell Biol*. 2024;25(5):379–395. doi:10.1038/s41580-023-00689-6
13. Ma W, Jiang X, Jia R, Li Y. Mechanisms of ferroptosis and targeted therapeutic approaches in urological malignancies. *Cell Death Discovery*. 2024;10(1):432. doi:10.1038/s41420-024-02195-w
14. Burdette BE, Esparza AN, Zhu H, Wang S. Gasdermin D in pyroptosis. *Acta pharmaceutica Sinica B*. 2021;11(9):2768–2782. doi:10.1016/j.apsb.2021.02.006
15. Yu P, Zhang X, Liu N, Tang L, Peng C, Chen X. Pyroptosis: mechanisms and diseases. *Signal Transduct Target Ther*. 2021;6(1):128. doi:10.1038/s41392-021-00507-5
16. Chen W, Zhang W, Zhou T, Cai J, Yu Z, Wu Z. A newly defined pyroptosis-related gene signature for the prognosis of bladder cancer. *Int J Gene Med*. 2021;14:8109–8120. doi:10.2147/IJGM.S337735
17. Fang Y, Tian S, Pan Y, et al. Pyroptosis: a new frontier in cancer. *Biomed Pharmacothe*. 2020;121:109595. doi:10.1016/j.biopha.2019.109595
18. Zhang ZH, Wang Y, Zhang Y, et al. The function and mechanisms of action of circular RNAs in urologic cancer. *Mol Cancer*. 2023;22(1):61. doi:10.1186/s12943-023-01766-2
19. Wang H, Zhou X, Li C, et al. The emerging role of pyroptosis in pediatric cancers: from mechanism to therapy. *J Hematol Oncol*. 2022;15(1):140. doi:10.1186/s13045-022-01365-6
20. Liang X, Qin Y, Wu D, Wang Q, Wu H. Pyroptosis: a double-edged sword in lung cancer and other respiratory diseases. *Cell Commun Signaling*. 2024;22(1):40. doi:10.1186/s12964-023-01458-w
21. Faria SS, Costantini S, de Lima VCC, et al. NLRP3 inflammasome-mediated cytokine production and pyroptosis cell death in breast cancer. *J Biomed Sci*. 2021;28(1):26. doi:10.1186/s12929-021-00724-8
22. Zhang C, Liu N. Ferroptosis, necroptosis, and pyroptosis in the occurrence and development of ovarian cancer. *Front Immunol*. 2022;13:920059. doi:10.3389/fimmu.2022.920059

23. Zhao Q, Feng H, Yang Z, et al. The central role of a two-way positive feedback pathway in molecular targeted therapies-mediated pyroptosis in anaplastic thyroid cancer. *Clin Translational Med*. 2022;12(2):e727. doi:10.1002/ctm2.727
24. Zou Z, Zhao M, Yang Y, et al. The role of pyroptosis in hepatocellular carcinoma. *Cellular Oncol*. 2023;46(4):811–823. doi:10.1007/s13402-023-00787-9
25. Wang S, Liao X, Xiong X, et al. Pyroptosis in urinary malignancies: a literature review. *Discov Oncol*. 2023;14(1):12. doi:10.1007/s12672-023-00620-7
26. Zychlinsky A, Prevost MC, Sansonetti PJ. Shigella flexneri induces apoptosis in infected macrophages. *Nature*. 1992;358(6382):167–169. doi:10.1038/358167a0
27. Cookson BT, Brennan MA. Pro-inflammatory programmed cell death. *Trends Microbiol*. 2001;9(3):113–114. doi:10.1016/S0966-842X(00)01936-3
28. Fink SL, Cookson BT. Apoptosis, pyroptosis, and necrosis: mechanistic description of dead and dying eukaryotic cells. *Infect Immun*. 2005;73(4):1907–1916. doi:10.1128/IAI.73.4.1907-1916.2005
29. Wang K, Sun Q, Zhong X, et al. Structural mechanism for GSDMD targeting by autoprocessed caspases in pyroptosis. *Cell*. 2020;180(5):941–955.e920. doi:10.1016/j.cell.2020.02.002
30. Shi J, Zhao Y, Wang K, et al. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. *Nature*. 2015;526(7575):660–665. doi:10.1038/nature15514
31. Ding J, Wang K, Liu W, et al. Pore-forming activity and structural autoinhibition of the gasdermin family. *Nature*. 2016;535(7610):111–116. doi:10.1038/nature18590
32. Lacey CA, Mitchell WJ, Dadelahi AS, Skyberg JA. Caspase-1 and caspase-11 mediate pyroptosis, inflammation, and control of Brucella joint infection. *Infect Immun*. 2018;86(9). doi:10.1128/IAI.00361-18
33. Galluzzi L, Vitale I, Aaronson SA, et al. Molecular mechanisms of cell death: recommendations of the nomenclature committee on cell death 2018. *Cell Death Differ*. 2018;25(3):486–541. doi:10.1038/s41418-017-0012-4
34. Jorgensen I, Rayamajhi M, Miao EA. Programmed cell death as a defence against infection. *Nat Rev Immunol*. 2017;17(3):151–164. doi:10.1038/nri.2016.147
35. Hsu SK, Li CY, Lin IL, et al. Inflammation-related pyroptosis, a novel programmed cell death pathway, and its crosstalk with immune therapy in cancer treatment. *Theranostics*. 2021;11(18):8813–8835. doi:10.7150/thno.62521
36. Tan Y, Chen Q, Li X, et al. Pyroptosis: a new paradigm of cell death for fighting against cancer. *J Experim Clin Cancer Res*. 2021;40(1):153. doi:10.1186/s13046-021-01959-x
37. Frank D, Vince JE. Pyroptosis versus necroptosis: similarities, differences, and crosstalk. *Cell Death Differ*. 2019;26(1):99–114. doi:10.1038/s41418-018-0212-6
38. Du T, Gao J, Li P, et al. Pyroptosis, metabolism, and tumor immune microenvironment. *Clin Translational Med*. 2021;11(8):e492. doi:10.1002/ctm2.492
39. Jing W, Lo Pilato J, Kay C, Man SM. Activation mechanisms of inflammasomes by bacterial toxins. *Cellular Microbiol*. 2021;23(4):e13309. doi:10.1111/cmi.13309
40. Zhaolin Z, Guohua L, Shiyuan W, Zuo W. Role of pyroptosis in cardiovascular disease. *Cell Proliferation*. 2019;52(2):e12563. doi:10.1111/cpr.12563
41. Shirasuna K, Karasawa T, Takahashi M. Exogenous nanoparticles and endogenous crystalline molecules as danger signals for the NLRP3 inflammasomes. *J Cell Physiol*. 2019;234(5):5436–5450. doi:10.1002/jcp.27475
42. Vasudevan SO, Behl B, Rathinam VA. Pyroptosis-induced inflammation and tissue damage. *Semin Immunopathol*. 2023;69:101781. doi:10.1016/j.smim.2023.101781
43. Shi J, Gao W, Shao F. Pyroptosis: gasdermin-mediated programmed necrotic cell death. *Trends Biochem Sci*. 2017;42(4):245–254. doi:10.1016/j.tibs.2016.10.004
44. Kovacs SB, Miao EA. Gasdermins: effectors of Pyroptosis. *Trends Cell Biol*. 2017;27(9):673–684. doi:10.1016/j.tcb.2017.05.005
45. Wei X, Xie F, Zhou X, et al. Role of pyroptosis in inflammation and cancer. *Cell Mol Immunol*. 2022;19(9):971–992. doi:10.1038/s41423-022-00905-x
46. Huang Y, Wang JW, Huang J, et al. Pyroptosis, a target for cancer treatment? *Apoptosis*. 2022;27(1–2):1–13. doi:10.1007/s10495-021-01703-y
47. Wei Y, Yang L, Pandeya A, Cui J, Zhang Y, Li Z. Pyroptosis-induced inflammation and tissue damage. *J Mol Biol*. 2022;434(4):167301. doi:10.1016/j.jmb.2021.167301
48. Yang D, He Y, Muñoz-Planillo R, Liu Q, Núñez G. Caspase-11 requires the pannexin-1 channel and the purinergic P2X7 pore to mediate pyroptosis and endotoxic shock. *Immunity*. 2015;43(5):923–932. doi:10.1016/j.immuni.2015.10.009
49. Rogers C, Fernandes-Alnemri T, Mayes L, Alnemri D, Cingolani G, Alnemri ES. Cleavage of DFNA5 by caspase-3 during apoptosis mediates progression to secondary necrotic/pyroptotic cell death. *Nat Commun*. 2017;8(1):14128. doi:10.1038/ncomms14128
50. Wang Y, Gao W, Shi X, et al. Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin. *Nature*. 2017;547(7661):99–103. doi:10.1038/nature22393
51. Orning P, Weng D, Starheim K, et al. Pathogen blockade of TAK1 triggers caspase-8-dependent cleavage of gasdermin D and cell death. *Science*. 2018;362(6418):1064–1069. doi:10.1126/science.aau2818
52. Sarhan J, Liu BC, Muendlein HI, et al. Caspase-8 induces cleavage of gasdermin D to elicit pyroptosis during Yersinia infection. *Proc Natl Acad Sci*. 2018;115(46):E10888–e10897. doi:10.1073/pnas.1809548115
53. Hou J, Zhao R, Xia W, et al. PD-L1-mediated gasdermin C expression switches apoptosis to pyroptosis in cancer cells and facilitates tumour necrosis. *Nat Cell Biol*. 2020;22(10):1264–1275. doi:10.1038/s41556-020-0575-z
54. Zhou Z, He H, Wang K, et al. Granzyme A from cytotoxic lymphocytes cleaves GSDMB to trigger pyroptosis in target cells. *Science*. 2020;368(6494). doi:10.1126/science.aaz7548
55. Liu Y, Fang Y, Chen X, et al. Gasdermin E-mediated target cell pyroptosis by CAR T cells triggers cytokine release syndrome. *Sci Immunol*. 2020;5(43). doi:10.1126/sciimmunol.aax7969
56. Zhang Z, Zhang Y, Xia S, et al. Gasdermin E suppresses tumour growth by activating anti-tumour immunity. *Nature*. 2020;579(7799):415–420. doi:10.1038/s41586-020-2071-9

57. Coll RC, Schroder K, Pelegrín P. NLRP3 and pyroptosis blockers for treating inflammatory diseases. *Trends Pharmacol Sci*. 2022;43(8):653–668. doi:10.1016/j.tips.2022.04.003
58. Evavold CL, Hafner-Bratkovič I, Devant P, et al. Control of gasdermin D oligomerization and pyroptosis by the Ragulator-Rag-mTORC1 pathway. *Cell*. 2021;184(17):4495–4511.e4419. doi:10.1016/j.cell.2021.06.028
59. Kambara H, Liu F, Zhang X, et al. Gasdermin D exerts anti-inflammatory effects by promoting neutrophil death. *Cell Rep*. 2018;22(11):2924–2936. doi:10.1016/j.celrep.2018.02.067
60. Kang R, Zeng L, Zhu S, et al. Lipid peroxidation drives Gasdermin D-mediated pyroptosis in lethal polymicrobial sepsis. *Cell Host Microbe*. 2018;24(1):97–108.e104. doi:10.1016/j.chom.2018.05.009
61. Zhang XW, Li L, Liao M, et al. Thermal proteome profiling strategy identifies CNPY3 as a cellular target of gambogic acid for inducing prostate cancer pyroptosis. *J Med Chem*. 2024;67(12):10005–10011. doi:10.1021/acs.jmedchem.4c00140
62. Zhang Y, Yang J, Wen Z, et al. A novel 3',5'-diprenylated chalcone induces concurrent apoptosis and GSDME-dependent pyroptosis through activating PKCδ/JNK signal in prostate cancer. *Aging*. 2020;12(10):9103–9124. doi:10.18632/aging.103178
63. Zeng Y, Li MX, Wu SQ, Xu C. Carvedilol induces pyroptosis through NLRP3-caspase1-ASC inflammasome by nuclear migration of NF-kappaB in prostate cancer models. *Mol Biol Rep*. 2024;51(1):201. doi:10.1007/s11033-023-09132-7
64. Xu Z, Wang H, Qin Z, et al. NLRP3 inflammasome promoted the malignant progression of prostate cancer via the activation of caspase-1. *Cell Death Discovery*. 2021;7(1):399. doi:10.1038/s41420-021-00766-9
65. Ponomareva L, Liu H, Duan X, et al. AIM2, an IFN-inducible cytosolic DNA sensor, in the development of benign prostate hyperplasia and prostate cancer. *Molecular Cancer Res*. 2013;11(10):1193–1202. doi:10.1158/1541-7786.MCR-13-0145
66. Ma Z, Zhang W, Dong B, et al. Docetaxel remodels prostate cancer immune microenvironment and enhances checkpoint inhibitor-based immunotherapy. *Theranostics*. 2022;12(11):4965–4979. doi:10.7150/thno.73152
67. Tian A, Wu T, Zhang Y, Chen J, Sha J, Xia W. Triggering pyroptosis enhances the antitumor efficacy of PARP inhibitors in prostate cancer. *Cellular Oncol*. 2023;46(6):1855–1870. doi:10.1007/s13402-023-00860-3
68. Li T, Liu N, Zhang G, Chen M. CASP4 and CASP8 as newly defined autophagy-pyroptosis-related genes associated with clinical and prognostic features of renal cell carcinoma. *J Cancer Res Ther*. 2022;18(7):1952–1960. doi:10.4103/jcrt.jcrt_126_22
69. Wu S, Wang B, Li H, et al. Targeting STING elicits GSDMD-dependent pyroptosis and boosts anti-tumor immunity in renal cell carcinoma. *Oncogene*. 2024;43(20):1534–1548. doi:10.1038/s41388-024-03013-4
70. Tan YF, Wang M, Chen ZY, Wang L, Liu XH. Inhibition of BRD4 prevents proliferation and epithelial-mesenchymal transition in renal cell carcinoma via NLRP3 inflammasome-induced pyroptosis. *Cell Death Dis*. 2020;11(4):239. doi:10.1038/s41419-020-2431-2
71. Zhang Y, Chen X, Fu Q, et al. Comprehensive analysis of pyroptosis regulators and tumor immune microenvironment in clear cell renal cell carcinoma. *Can Cell Inter*. 2021;21(1):667. doi:10.1186/s12935-021-02384-y
72. Zhang X, Wei X, Wang Y, et al. Pyroptosis regulators and tumor microenvironment infiltration characterization in clear cell renal cell carcinoma. *Front Oncol*. 2021;11:774279. doi:10.3389/fonc.2021.774279
73. Zhu A, Cheng C, Lin S, et al. Silence of linc00023 inhibits pyroptosis and promotes cell proliferation via regulating p53. *Gene*. 2023;882:147628. doi:10.1016/j.gene.2023.147628
74. Lobo N, Afferi L, Moschini M, et al. Epidemiology, screening, and prevention of bladder cancer. *European Urol Oncol*. 2022;5(6):628–639. doi:10.1016/j.euo.2022.10.003
75. Gunassekaran GR, Poongkavithai Vadevoo SM, Baek MC, Lee B. M1 macrophage exosomes engineered to foster M1 polarization and target the IL-4 receptor inhibit tumor growth by reprogramming tumor-associated macrophages into M1-like macrophages. *Biomaterials*. 2021;278:121137. doi:10.1016/j.biomaterials.2021.121137
76. Lalonde E, Ishkanian AS, Sykes J, et al. Tumour genomic and microenvironmental heterogeneity for integrated prediction of 5-year biochemical recurrence of prostate cancer: a retrospective cohort study. *Lancet Oncol*. 2014;15(13):1521–1532. doi:10.1016/S1470-2045(14)71021-6
77. Luo CG, Gui CP, Huang GW, et al. Identification of ZDHHC1 as a pyroptosis inducer and potential target in the establishment of pyroptosis-related signature in localized prostate cancer. *Oxid Med Cell Longev*. 2022;2022:5925817. doi:10.1155/2022/5925817
78. Wang H, He Z, Gao Y, et al. Dual-pronged attack: pH-driven membrane-anchored NIR dual-type nano-photosensitizer excites immunogenic pyroptosis and sequester immune checkpoint for enhanced prostate cancer photo-immunotherapy. *Adv Sci*. 2023;10(28):e2302422. doi:10.1002/advs.202302422
79. Yu X, Liao B, Du Z, Zhu P. EGFR/TKIs induce excessive apoptosis of bladder carcinoma cells by arresting cell cycle and promoting mitochondrial peroxidation damage. *Cellular Molecular Biol*. 2024;70(5):258–262. doi:10.14715/cmb/2024.70.5.38
80. Sloas C, Gill S, Klichinsky M. Engineered CAR-macrophages as adoptive immunotherapies for solid tumors. *Front Immunol*. 2021;12:783305. doi:10.3389/fimmu.2021.783305
81. Guo P, Dai P, Yang S, et al. Engineered macrophages tune intratumoral cytokines through precisely controlled self-pyroptosis to enhance bladder cancer immunotherapy. *Small*. 2024;20(13):e2306699. doi:10.1002/smll.202306699
82. Cheng B, Tang C, Xie J, et al. Cuproptosis illustrates tumor micro-environment features and predicts prostate cancer therapeutic sensitivity and prognosis. *Life Sci*. 2023;325:121659. doi:10.1016/j.lfs.2023.121659
83. Li X, Bai Y, Feng K, et al. Therapeutic, diagnostic and prognostic values of TRIM proteins in prostate cancer. *Pharmacol Reports*. 2023;75(6):1445–1453. doi:10.1007/s43440-023-00534-9
84. Stafford MYC, Willoughby CE, Walsh CP, McKenna DJ. Prognostic value of miR-21 for prostate cancer: a systematic review and meta-analysis. *Biosci Rep*. 2022;42(1). doi:10.1042/BSR20211972
85. Hu D, Cao Q, Tong M, et al. A novel defined risk signature based on pyroptosis-related genes can predict the prognosis of prostate cancer. *BMC Med Genomics*. 2022;15(1):24. doi:10.1186/s12920-022-01172-5
86. Fu J, Li G, Luo R, Lu Z, Wang Y. Classification of pyroptosis patterns and construction of a novel prognostic model for prostate cancer based on bulk and single-cell RNA sequencing. *Front Endocrinol*. 2022;13:1003594. doi:10.3389/fendo.2022.1003594
87. Mickley A, Kovaleva O, Kzhyshkowska J, Gratchev A. Molecular and immunologic markers of kidney cancer-potential applications in predictive, preventive and personalized medicine. *EPMA J*. 2015;6(1):20. doi:10.1186/s13167-015-0042-2
88. Rosellini M, Marchetti A, Mollica V, Rizzo A, Santoni M, Massari F. Prognostic and predictive biomarkers for immunotherapy in advanced renal cell carcinoma. *Nat Rev Urol*. 2023;20(3):133–157. doi:10.1038/s41585-022-00676-0

89. Michaelson MD, Stadler WM. Predictive markers in advanced renal cell carcinoma. *Semin Oncol*. 2013;40(4):459–464. doi:10.1053/j.seminoncol.2013.05.001
90. Ma J, Kang Z, Yang G, et al. Pyroptosis-related subtypes predict the response of clear cell renal cell carcinoma to targeted therapy. *Front Biosci*. 2023;28(12):334. doi:10.31083/j.fbl2812334
91. Khan M, Ai M, Du K, et al. Pyroptosis relates to tumor microenvironment remodeling and prognosis: a pan-cancer perspective. *Front Immunol*. 2022;13:1062225. doi:10.3389/fimmu.2022.1062225
92. Sun X, Yang Y, Meng X, Li J, Liu X, Liu H. PANoptosis: mechanisms, biology, and role in disease. *Immunol Rev*. 2024;321(1):246–262. doi:10.1111/imr.13279
93. Jiang Z, Wang J, Dao C, et al. Utilizing a novel model of PANoptosis-related genes for enhanced prognosis and immune status prediction in kidney renal clear cell carcinoma. *Apoptosis*. 2024;29(5–6):681–692. doi:10.1007/s10495-023-01932-3
94. Bertheloot D, Latz E, Franklin BS. Necroptosis, pyroptosis and apoptosis: an intricate game of cell death. *Cell Mol Immunol*. 2021;18(5):1106–1121.
95. Fu L, Bao J, Li J, et al. Crosstalk of necroptosis and pyroptosis defines tumor microenvironment characterization and predicts prognosis in clear cell renal carcinoma. *Front Immunol*. 2022;13:1021935. doi:10.3389/fimmu.2022.1021935
96. Kumar D, Gurrapu S, Wang Y, et al. LncRNA Malat1 suppresses pyroptosis and T cell-mediated killing of incipient metastatic cells. *Nat Cancer*. 2024;5(2):262–282. doi:10.1038/s43018-023-00695-9
97. Liu C, Dai S, Geng H, et al. Development and validation of a kidney renal clear cell carcinoma prognostic model relying on pyroptosis-related LncRNAs-A multidimensional comprehensive bioinformatics exploration. *Eur J Med Res*. 2023;28(1):341. doi:10.1186/s40001-023-01277-2
98. Deng D, Liu F, Liu Z, et al. Robust pyroptosis risk score guides the treatment options and predicts the prognosis of bladder carcinoma. *Front Immunol*. 2022;13:965469. doi:10.3389/fimmu.2022.965469
99. Du X, Zhao X, Tang Y, Tang W. Construction of pyroptosis-related prognostic and immune infiltration signature in bladder cancer. *Dis Markers*. 2022;2022:6429993. doi:10.1155/2022/6429993
100. Zhang Q, Tan Y, Zhang J, et al. Pyroptosis-related signature predicts prognosis and immunotherapy efficacy in muscle-invasive bladder cancer. *Front Immunol*. 2022;13:782982. doi:10.3389/fimmu.2022.782982
101. Lu Z, Tang F, Li Z, et al. Prognosis risk model based on pyroptosis-related lncRNAs for bladder cancer. *Dis Markers*. 2022;2022:7931393. doi:10.1155/2022/7931393
102. Lu H, Wu J, Liang L, Wang X, Cai H. Identifying a novel defined pyroptosis-associated long noncoding RNA signature contributes to predicting prognosis and tumor microenvironment of bladder cancer. *Front Immunol*. 2022;13:803355. doi:10.3389/fimmu.2022.803355
103. Zhong X, Zeng H, Zhou Z, et al. Structural mechanisms for regulation of GSDMB pore-forming activity. *Nature*. 2023;616(7957):598–605. doi:10.1038/s41586-023-05872-5
104. Chen X, Chen H, Yao H, et al. Turning up the heat on non-immunoreactive tumors: pyroptosis influences the tumor immune microenvironment in bladder cancer. *Oncogene*. 2021;40(45):6381–6393. doi:10.1038/s41388-021-02024-9