Review article

The Implications of Pyroptosis in Conditions Affecting the Genitourinary Tract

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Abstract

Pyroptosis, a unique form of programmed cell death distinct from apoptosis and necrosis, is thought to be closely associated with the pathogenesis of various diseases. Although there has been considerable attention given to the relationship between pyroptosis and urinary diseases, a comprehensive review on this subject is currently lacking. The objective of this study is to address this gap by investigating the involvement of pyroptosis in the development and progression of both benign urinary diseases and urinary malignancies. Through this thorough examination, it has been determined that pyroptosis plays a significant role in the pathogenesis of urinary diseases. In summary, this review not only offers valuable insights for future research directions but also proposes innovative approaches for utilizing pyroptosis as a powerful tool in combating urinary diseases.

Keywords: Pyroptosis; acute kidney injury (AKI); diabetic nephropathy (DN); prostatic hyperplasia (BPH); genitourinary tract

Abbreviations

ASC: Caspase-recruitment domain

ROS: Reactive oxygen species

IL-18: Interleukin-18

IL-1β: Interleukin-1β

LPS: Lipopolysaccharide

TAK1: TGF-β-activated kinase-1

GSDMA: Gasdermin A

GSDMB: Gasdermin B

 GSDMC: Gasdermin C

GSDMD: Gasdermin D

GSDME: Gasdermin E

 GZMB: Granzyme B

GZMA: Granzyme A

USF2: Upstream stimulatory factor 2

THBS1: Thrombospondin-1

NLRP1: NOD-like receptor 1

AIM2: Absent in melanoma 2

NLRP3: NOD-like receptor 3

HMGB1: High mobility group box 1

ERS: Endoplasmic reticulum stress

TLR2: Toll-like receptor 2

ROCK1: Rho-associated coiled-coil containing protein kinase-1

TXNIP: Thioredoxin–interacting protein miR-93

MicroRNA-93 PRDX3: Peroxiredoxin 3

STAT3: Transcription 3

HK2: Hexokinase 2

LDHA: Lactate dehydrogenase A

ENO2: Enolase 2

USP24 :Ubiquitin-specifc peptidase 24

IGFBP3: Insulin-like growth factor-binding protein 3

Introduction

Pyroptosis, a form of programmed cell death that has been recently discovered, is classified as an inflammatory programmed cell death (PCD) [1]. Its initial description dates back to 1992, but the term "pyroptosis" was coined in 2001 when it was observed that macrophages infected with bacteria underwent rapid lytic cell death, which was found to be dependent on caspase-1 activity [2]. Recent research has indicated that macrophages not only regulate pyroptosis but also play a crucial role in the development of acute kidney injury (AKI), diabetic nephropathy (DN), and renal fibrosis. Pyroptosis is characterized by the formation of pores in the cell membrane, cell swelling, and the release of inflammatory intracellular contents [3]. The release of inflammatory factors, such as interleukin-1β (IL-1β) and interleukin-18 (IL-18), during cell lysis amplifies the inflammatory effects and activates immune responses [4]. The discovery of the gasdermin D (GSDMD) protein has provided insights into the underlying mechanism of pyroptosis. Shi et al. demonstrated that caspase-1/11/4/5 can induce pyroptosis by cleaving GSDMD and releasing its N-terminal domain [5].

In addition to GSDMD, the gasdermin family comprises five other members. In humans, the gasdermin family includes GSDMA, GSDMB, GSDMC, GSDMD, GSDME/DFNA5, and PVJK/DFNB59. In mice, there are five gasdermin members, namely GSDMA, GSDMC, GSDMD, GSDME, and PJVK/DFNB59, with the absence of GSDMB. All gasdermins, except DFNB59, possess two conserved domains: an N-terminal effector domain and a C-terminal inhibitory domain. Under normal circumstances, moderate pyroptosis plays a significant role in the host's defense against pathogen infections. However, when pyroptosis becomes excessive, it can lead to uncontrolled inflammatory responses, extensive cell death, and severe tissue damage, which in turn can result in the development of inflammatory or autoimmune diseases. As a form of cell death that triggers inflammation, pyroptosis presents a promising avenue for harnessing the anti-tumor immune response and potentially eliminating cancer. Numerous studies have highlighted the pivotal role of pyroptosis in various types of cancer, such as breast cancer, gastric cancer, and lung cancer [6].

In this article, we aim to provide a comprehensive overview of the different signaling pathways involved in pyroptosis, allowing for a deeper understanding of the molecular mechanisms underlying this process. Furthermore, we delve into the specific role of pyroptosis in urinary diseases and propose potential directions for future research in this area. The conventional pyroptosis pathway is regulated by caspase-1. Inflammasomes are composed of pattern-recognition receptors (PRRs), also known as inflammasome sensors, apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC), and inactive pro-caspase-1. PRRs have the ability to identify pathogen-associated molecular patterns and danger-associated molecular patterns (PAMPs and DAMPs) [7]. NLRs, such as NLRP1, NLRP3, and NLRC4, AIM2, and pyrin are included in the PRRs [8]. NLRs typically consist of a leucine-rich repeat (LRR), a nucleotide-binding oligomerization domain (NACHT/NOD), and a caspase-recruitment domain (CARD) or pyrin domain (PYD) and are categorized into NLRPs or NLRCs based on the presence of a PYD or CARD at their N-terminus [9].

A PYD is essential for interaction with ASC. The NOD is involved in ATP-dependent activation of the signal [10]. The LRR is responsible for recognizing ligands and autoinhibition. The CARD is involved in recruiting pro-caspase-1. Upon receiving a stimulating signal, inflammasome sensors recruit pro-caspase-1 (which contains a CARD) either directly through homotypic binding of CARD or indirectly through the PYD via ASC, which has a PYD and a CARD. Subsequently, caspase-1 activation occurs through

self-cleavage [11]. Activated caspase-1 not only cleaves inactive IL-1β and IL-18 precursors but also cleaves GSDMD to generate GSDMD-NT and GSDMD-CT. GSDMD-N creates pores in the plasma membrane, resulting in cell swelling and pyroptosis [12]. Most gram-negative bacteria induce the non-canonical inflammasome pathway. In humans, this nonclassical signaling pathway is triggered by caspase-4 and caspase-5, while in mice, it is mediated by caspase-11. These caspases are activated through direct interaction with lipopolysaccharide (LPS) [13]. Once activated, caspase-4/5/11 cleaves GSDMD, leading to the promotion of pyroptosis.

However, these caspases are unable to cleave pro-IL-18/pro-IL-1β but can cleave GSDMD, resulting in K+ efflux and activation of the NLRP3/caspase-1 pathway. This cascade ultimately leads to the maturation and release of interleukin-18 (IL-18) and interleukin-1β (IL-1β) [14]. The apoptotic caspase-mediated pathway, along with the inflammatory caspase-1/4/5/11, can also trigger pyroptosis. Chemotherapeutic drugs have the ability to induce caspase-3 to cleave GSDME, resulting in the formation of GSDME-N termini, which in turn cause pyroptosis [15]. Moreover, pathogenic Yersinia has been observed to inhibit TGFβ-activated kinase-1 (TAK1) through the Yersinia effector protein YopJ, leading to caspase-8-related cleavage of GSDMD and the subsequent initiation of pyroptosis [16]. Interestingly, caspase-8 induces GSDMC cleavage, thereby activating a non-canonical pyroptosis pathway in cancer cells [17] (Figure 1).
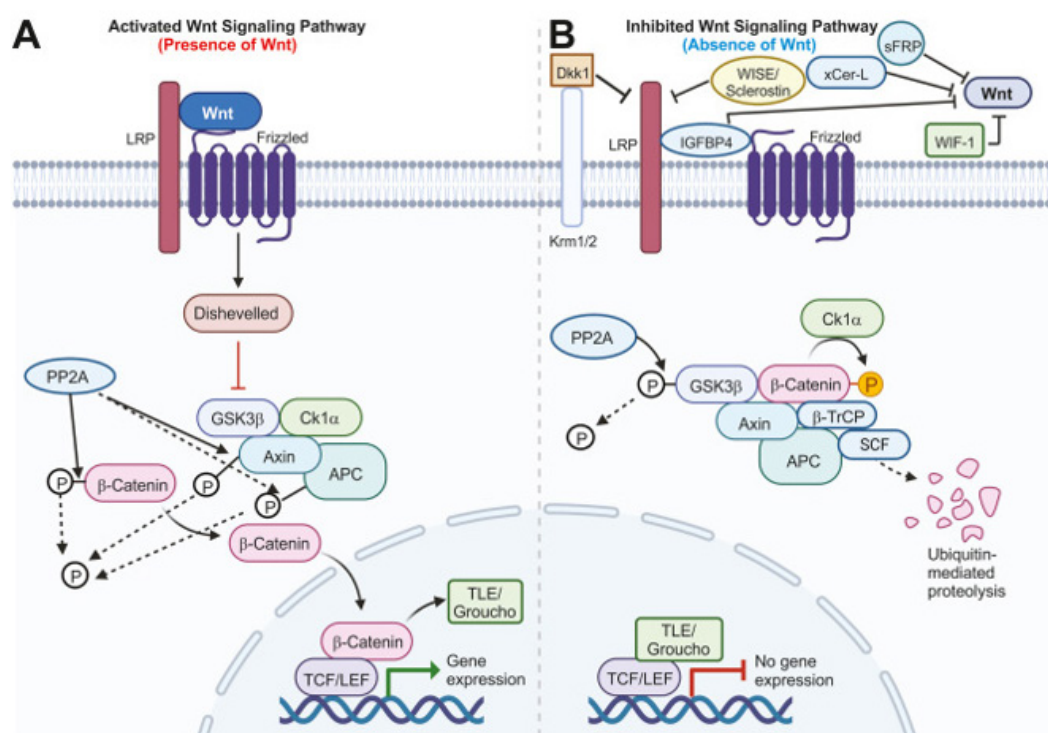

Figure 1:

On the other hand, the granzyme-mediated pathway involves the serine protease Granzyme A (GzmA), which has long been recognized as a mediator of cell death within the granzyme family. Zhou et al. discovered that GZMA, derived from cytotoxic T lymphocytes, cleaves GSDMB to induce pyroptosis [18]. In 2020, it was reported that CAR-T cells release granzyme B (GzmB), which activates caspase-3 and subsequently triggers the caspase-3/GSDME-mediated pyroptotic pathway, leading to pyroptosis [19]. Additionally, Zhang et al. found that GzmB directly cleaves GSDME, inducing pyroptosis and enhancing anti-tumor immunity while inhibiting tumor growth [20] (Figure 1).

Pyroptosis in Benign Urinary Diseases

Pyroptosis, a form of programmed cell death, has been found to play a significant role in the development of various benign urinary diseases. One such disease is interstitial cystitis (IC), also known as bladder pain syndrome (BPS) [21]. IC is a chronic pain disorder that primarily affects the bladder, pelvis, or abdomen [22]. Studies have shown that the NLRP3 inflammasome, a multiprotein complex involved in the activation of inflammatory responses, is a crucial player in the development of IC. Elevated expression levels of NLRP3, caspase-1, and GSDMD have been observed in patients with IC [23]. Wang et al. discovered that the NLRP3/GSDMD-N

pathway is activated and contributes to the development of IC. Additionally, they found that aster tataricus extract (ATE) can serve as an inhibitor of NLRP3, offering a potential treatment option for IC. The identification of the NLRP3/caspase-1/GSDMD-N pathway as a novel mechanism provides a promising direction for further research on IC [24]. In the case of benign prostatic hyperplasia (BPH), a condition characterized by the nonmalignant overgrowth of prostatic tissue surrounding the urethra, pyroptosis also appears to be involved.
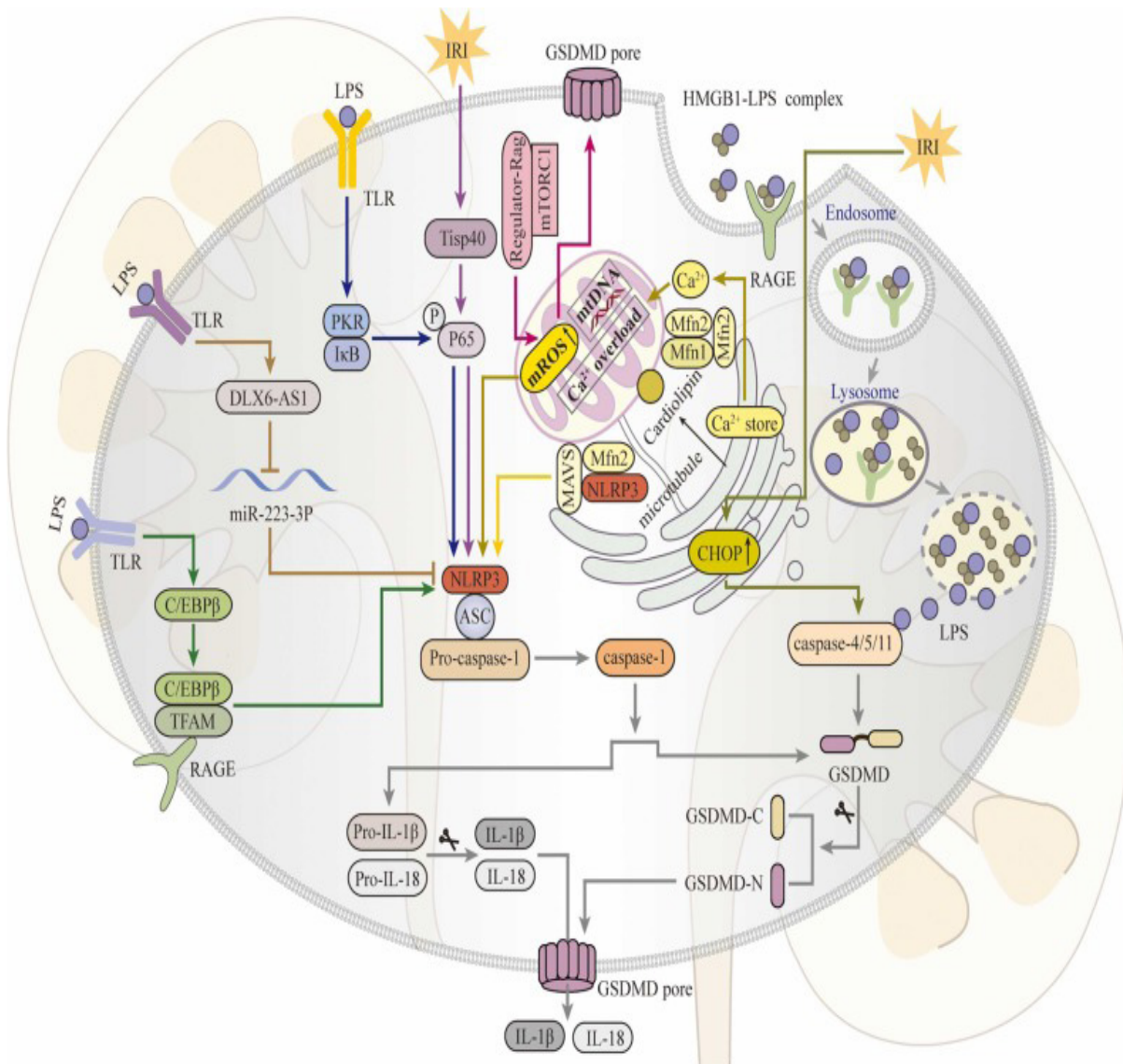

Figure 2:

BPH leads to the constriction of the urethral opening, resulting in lower urinary tract symptoms (LUTS) such as urgency, frequency, nocturia, incomplete bladder emptying, and a weak urine stream [25]. Inflammation has been identified as a key factor in the development of BPH. Studies have shown elevated expression levels of NLRP1, caspase-1, IL-18, and IL-1β in BPH. This suggests that the NLRP1/caspase-1 pathway is activated and contributes to the pathogenesis of BPH. Further research is needed to fully understand the role of pyroptosis in BPH and explore potential therapeutic interventions targeting this pathway [26]. Jiang and colleagues discovered that peroxiredoxin 3 (PRDX3) inhibits autophagy flux and triggers pyroptosis, leading to inflammatory reactions and promoting prostate tissue overgrowth. Recent findings suggest that the levels of AIM2 mRNA are higher in benign prostatic hyperplasia (BPH) tissue compared to normal prostate tissue. AIM2 recruits ASC and pro-caspase-1 to form the AIM2 inflammasome, resulting

in cell swelling and pyroptosis [27]. These investigations have aided in identifying potential therapeutic targets for BPH. The signaling pathways that regulate pyroptosis in BPH are illustrated in Figure 3.

Pyroptosis in Acute Kidney Injury (AKI)

Acute kidney injury (AKI) is characterized by a sudden rise in serum creatinine, a reduction in urine output, or both. Recent studies have highlighted the involvement of pyroptosis in AKI. Sun et al. observed high expression levels of thrombospondin-1 (THBS1) and upstream stimulatory factor 2 (USF2) in patients with sepsis-induced AKI. USF2 upregulates THBS1 expression, activating the TGF-β/Smad3/NLRP3/caspase-1 pathway and promoting pyroptosis, worsening sepsis-induced AKI. Miao et al. noted a significant increase in GSDMD expression in both cisplatin-induced and ischemia-reperfusion (I/R) AKI models [28]. Knocking out caspase-11 or GSDMD reduced kidney damage in mice with cisplatin-induced AKI. A 2020 study revealed elevated levels of high mobility group box 1 (HMGB1), IL-1β, IL-18, NLRP3, and GSDMD proteins in an AKI model. Hence, it is proposed that the HMGB1/NLRP3/GSDMD pathway plays a crucial role in AKI pathogenesis. Additionally, Li et al. demonstrated that the ROS/NLRP3/caspase-1/ GSDMD pathway mediates contrast-induced AKI (CI-AKI) through pyroptosis, and treatment with baicalin reduced inflammation and oxidative stress levels.

Furthermore, research has indicated that macrophage-derived exosomal miRNAs have significant implications in AKI [29]. The suppression of caspase-3 resulted in the prevention of GSDME-N cleavage, leading to the reduction of cisplatin-induced pyroptosis and kidney dysfunction. As a result, the caspase-3/GSDME-induced pyroptosis is a significant factor in the development of acute kidney injury (AKI). Juan et al. identified that the exosomal miR-93/thioredoxin-interacting protein (TXNIP) signaling pathway is crucial in the advancement of sepsis-induced AKI, with M1 exosomes promoting pyroptosis and M2 exosomes inhibiting it [30]. It is widely recognized that Rho-associated coiled-coil containing protein kinase-1 (ROCK1) plays a vital role in various pathological processes, including pyroptosis, inflammation, and endoplasmic reticulum stress (ERS). Wang et al. demonstrated that ROCK1 regulates LPS-induced kidney cell pyroptosis through Toll-like receptor 2 (TLR2)-mediated ERS, thereby hastening the progression of sepsis-induced AKI [31]. The signaling pathways that control pyroptosis in AKI are illustrated in Figure 2.
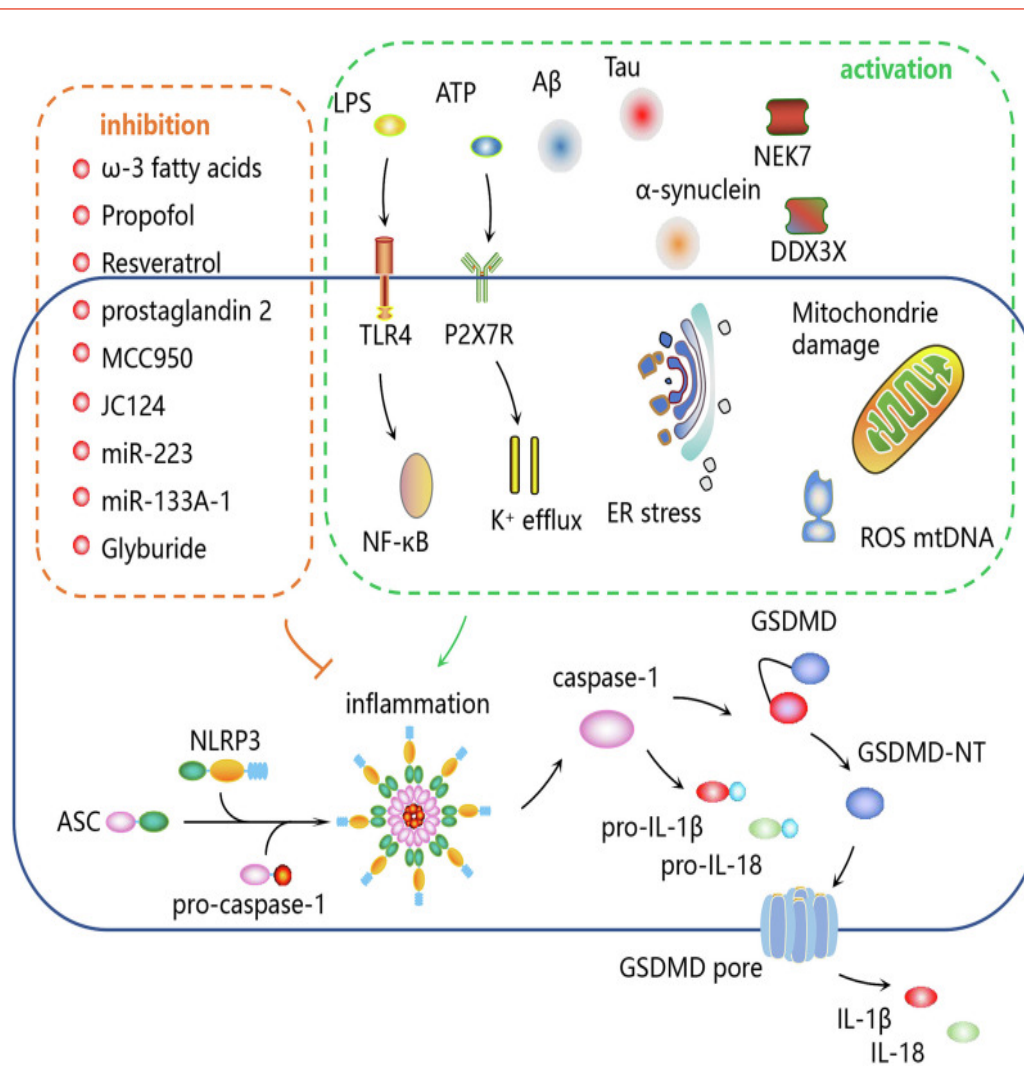

Figure 3:

Pyroptosis in Diabetic Nephropathy

Diabetic nephropathy (DN), also known as diabetic kidney disease (DKD), is a common and severe long-term microvascular complication that arises from damage to the renal glomeruli and tubules. Extensive evidence suggests that chronic inflammation contributes to the development of DN [32]. The involvement of pyroptosis signaling pathways in the progression of DN has become a focal point for researchers and healthcare professionals [33]. In 2020, it was revealed that the TXNIP/NLRP3 axis serves as a critical pathway in the regulation of DN through pyroptosis. Additionally, Ke et al. discovered that the endoplasmic reticulum stress-related factor IRE1α upregulates TXNIP/NLRP3 inflammasome-induced pyroptosis in DN rats [34]. Li et al. made an important discovery regarding the NLRP3/caspase-1/GSDMD signaling pathway in diabetic nephropathy (DN). They found that this pathway was significantly upregulated, leading to a dramatic increase in the secretion of IL-1β and IL-18 in DN mice [35]. Furthermore, they confirmed that SYR, a specific treatment, effectively inhibited the NLRP3/caspase-1/GSDMD pyroptosis pathway by upregulating NRF2 signaling in DN [36].

In another study by Li et al., it was observed that the expression of p-NF-κB, ASC, cleaved-IL-1β, NLRP3, cleaved-caspase-1, and GSDMD-N was elevated in a DN mouse model [37]. Additionally, they confirmed that geniposide (GE) could inhibit the development of DN through the APMK/SIRT1/NF-κB pathway [38]. This suggests that the APMK/SIRT1/NF-κB axis could potentially serve as a new signaling pathway for the treatment of DN. Moreover, the activation of the NLRP3 inflammasome has been implicated in the pathogenesis of DN. Wang et al. demonstrated that under high glucose conditions, the expression of NLRC4, IL-1β, and IL-18 was increased, leading to pyroptosis in renal tubular epithelial cells [39]. Additionally, Komada et al. showed that the activation of the AIM2 inflammasome by DNA from necrotic cells contributes to chronic kidney injury and pyroptosis [40]. Furthermore, Cheng et al. provided evidence that caspase-11/4- and GSDMD-mediated pyroptosis were activated in a DN mouse model and were involved in the development of DN [41]. These findings collectively confirm the significant roles of pyroptosis and inflammasomes in renal injury, ultimately impacting the pathogenesis of DN.

Pyroptosis in Urinary Tract Cancers

Urinary tract cancers, particularly bladder cancer, are prevalent malignancies [42]. Recent research has highlighted the significant role of pyroptosis in the development and progression of bladder cancer. For instance, He et al. discovered that GSDMB interacts with STAT3, leading to increased phosphorylation of STAT3. This, in turn, upregulates the expression of key glycolytic enzymes such as HK2, LDHA, ENO2, and IGFBP3, promoting glycolysis and cancer cell proliferation in bladder cancer cells [43]. Furthermore, their study revealed that USP24 binds to GSDMB, preventing its degradation in bladder cancer cells [44]. Consequently, the USP24/GSDMB/STAT3 axis emerges as a potential targetable signaling pathway for bladder cancer therapy. Chen et al. demonstrated through Kaplan-Meier curves that high levels of GSDMB and CASP6 are associated with improved prognoses in bladder cancer patients [45]. They also observed that tumors with elevated GSDMB and CASP6 expression were characterized by immune-inflammation, while those with low levels were immune-desert tumors. Additionally, they elucidated the crucial roles of GSDMB and CASP6 in immune infiltration [46].

El-Gamal et al.'s findings indicated that GSDMD expression is significantly higher in muscle-invasive bladder cancer (MIBC) compared to non-muscle-invasive bladder cancer (NMIBC) and control groups [47]. This suggests the involvement of GSDMD in the pathogenesis of bladder cancer and muscle invasion, with potential implications for predicting local tumor recurrence based on tissue expression levels [48]. Moreover, Peng et al. discovered that CD147 promotes cell proliferation in bladder cancer by upregulating GSDMD expression [49]. Pyroptosis, a form of programmed cell death, has also been implicated in the development of prostate cancer (PCa). The caspase-1 pathway, a classical pyroptosis pathway, plays a significant role in PCa [50]. NLRP3, a protein involved in physiological and pathological processes, including tumor progression, has been found to be elevated in PCa tissues and cell lines. This elevation is positively correlated with the expression of caspase-1 [51]. The NLRP3 inflammasome, activated by NLRP3, has been shown to promote tumor growth in PCa by activating caspase-1.

Additionally, NLRP12, another protein, has been found to be significantly higher in PCa tissue compared to adjacent benign tissue. NLRP12 is believed to play a crucial role in activating NF-κB and IL-1β signaling, contributing to the pathogenesis and progression of PCa [52]. It has been observed that NLRP12 can upregulate caspase-1, IL-1β, and IL-18, thereby promoting the occurrence and progression of PCa. Furthermore, studies have demonstrated the involvement of lipopolysaccharide (LPS) in the proliferation, migration, and invasion of PCa cells. LPS activates the caspase-4/5/11 pathway, leading to pyroptosis induction. However, the role of LPS-mediated pyroptosis in PCa is still under investigation. Moving on to renal cell carcinoma (RCC), it accounts for a small percentage of malignant diseases in adults. RCC is the seventh most common cancer in men and the ninth most common in women. The most prevalent type of RCC is clear cell RCC (ccRCC), followed by papillary RCC and chromophobe RCC. In recent years, the relationship between pyroptosis and the development of RCC has been extensively studied.

Cui et al. conducted a study and discovered that the expression of GSDMB was significantly higher in ccRCC tissues compared to the surrounding normal tissues. Furthermore, they confirmed that the upregulation of GSDMB was strongly associated with immune infiltrates and poor survival in ccRCC . These findings suggest that GSDMB has the potential to serve as a biomarker for poor prognosis and a potential target for immune therapy in ccRCC. Liver X receptors (LXRs), specifically nuclear receptor subfamily 1, group H, member 2 (NR1H2 or LXRB) and nuclear receptor subfamily 1, group H, member 3 (NR1H3 or LXRA), belong to the nuclear receptor superfamily and are expressed in various cells. Wang et al. conducted a study and found that the expression levels of NLRP3, a key component of the NLRP3 inflammasome, were

significantly lower in ccRCC tissue compared to normal kidney tissue. They also discovered that LXRα promoted tumor metastasis by downregulating the NLRP3 inflammasome in ccRCC [53].

Additionally, the inhibition of bromodomain-containing 4 (BRD4) has been shown to prevent cell proliferation and epithelial-mesenchymal transition (EMT), playing an anti-tumor role in RCC. This is achieved by activating the NF-κB-NLRP3-caspase-1 pyroptosis signaling pathway [54]. Zhang et al. found that the expression of most pyroptosis regulatory genes is positively correlated and plays a significant prognostic role in ccRCC [55]. AIM2, a protein involved in the innate immune response, has been found to play a crucial role in the development of various tumors. Recent studies have shown that AIM2 is highly expressed in ccRCC and promotes tumor development through immune activation pathways Tang et al. conducted a study and discovered that a long non-coding RNA called FOXD2 adjacent opposite strand RNA 1 (FOXD2-AS1) affects the expression of GSDMB and NLRP1. Interestingly, they also found that downregulating the expression of FOXD2-AS1 reduced the proliferation and migration of ccRCC cells [56-64].

Conclusion

Pyroptosis is a recently discovered type of cell death that is controlled by gasdermin proteins, typically activated by caspases. It plays a critical role in the onset, progression, and advancement of urological conditions. Further comprehensive exploration of pyroptosis in urological disorders will enhance our comprehension of diagnosing and treating urinary ailments. There is an urgent need for additional research to conduct more clinical trials and investigate the potential therapeutic applications of pyroptosis in urinary diseases.

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