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Prevalence Around Inflammatory Caspases in Urinary Tract Infections, Review

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Caspases are cysteinyl aspartate-specific proteases that play important roles in apoptosis, pyroptosis and cytokine maturation. Pyroptosis is a manifestation of inflammatory caspase mediated cell death induced by inflammatory caspases such as caspase-11, caspase 4, caspase 5 and caspase 1. These inflammatory caspases are involved in the inflammatory responses induced by these pathogens to control protozoan, viral, fungal and bacterial pathogen. This study aimed to understand the mechanism that involve different inflammatory caspases and their responses to urinary tract infections. By understanding the molecular pathways involved, we may be able to emphasize the specificity of inflammatory caspases. To acknowledge the physiological role of inflammatory caspases in the pathological processes, the recognition of the domestic substrate of these inflammatory caspases, which ultimately leads to pyroptosis must be recognized.

Keywords : Inflammatory Caspases, NACHT leucin-rich repeat PYD protein 3 (NLRP3), Pathogenesis, Pyroptosis, Urinary tract Infection (UTI), Uropathogenic *Escherichia coli* (UPEC).

One of the most prevalent infections in humans is urinary tract infection (UTI), which is mainly caused by uropathogenic *Escherichia coli* (UPEC) [1]. UTIs can be interpreted as the characteristic presence of pathogens in the urinary tract, such as the kidneys, bladder, ureters, and urethra[1,2,3]. It is a multifactorial disease that depends on factors such as age, family and individual history of patients, medical complications, and sexual activity. According to projections, 50% of women will have UTI at least once in their lifetime. A higher chance of recurrence within 3–4 months appears to be present in women with a history of UTIs. Women are at greater risk than men because of the short urethra. The incidence of UTIs increases with age. In every age group, the major problem in treating UTIs is disease recurrence[4,5,6,7] owing to the emergence of multidrug-resistant strains[8,9,10,11]. UTIs are classified mainly into cystitis and pyelonephritis based on the top and bottom urinary tract infections. Cystitis, prostatitis, and urethritis are upper urinary tract infections with many host risk factors, such as antibiotic use, sexual activity, family history,

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and postmenopausal age[12] Pyelonephritis (acute, chronic, and interstitial) perirenal and renal blisters are lower urinary tract infections of the kidney with associated host risk factors such as pregnancy, diabetes mellitus, catheterization, and a weak immune defense system[12]. Both upper and lower UTI are further divided into complicated and uncomplicated UTIs. Uncomplicated UTIs usually occur in persons with no structural or functional abnormalities in the urinary tract and no significant comorbidities that can result in serious outcomes in the future, and who are otherwise healthy. UTIs can be complicated if they are associated with pregnancy, structural and functional abnormalities, obstruction in urine flow, comorbidities such as poorly controlled diabetes, immunosuppression, indwelling catheters, and exposure to antibiotics. Complicated UTIs increase the risk of further infection in the patient's body. Catheter-associated urinary tract infections are a major cause of bloodstream infection.

The major causative pathogens of urinary tract infections are bacteria (gram-positive and gram-negative) and a few fungal species. The uropathogenic *Escherichia coli* (UPEC) account for more than 80% infection in urinary tract and involved in both complicated and uncomplicated infections[13,14]. Other pathogen besides UPEC causing uncomplicated UTIs are *Proteus mirabilis, Group B Streptococcus* (GBS), *Pseudomonas aeruginosa, Staphylococcus saprophyticus, Enterococcus faecalis, Klebsiella pneumoniae, Staphylococcus aureus* and *Candida spp*[15,16,17]. Complicated UTIs are associated with *Candida* spp, *Proteus mirabilis, Pseudomonas aeruginosa, Klebsiella pneumoniae,* GBS, *Enterococcus faecalis, Staphylococcus aureus, Enterococcus faecium*[18,19,20]. The most common treatment given to the UTIs patients are antibiotics and the long-term use of these leads to the emergence of multidrug resistance (MDR). In addition to the long-term dependency on antibiotics, it also alters the microbiota of the gastrointestinal tract and vagina. Due to these UTIs, uropathogens can easily overcome innate immune surveillance mechanisms and colonize the urinary tract via different mechanisms. To understand Urinary Tract Infection, one needs to understand the process of infection and inflammatory responses. Upon interaction with the pathogen or stimulation from external stimuli, the innate immune defense structure is activated and inflammation initiates the inflammatory process involved in urinary tract infections. Inflammasomes serve as effectors and sensors of the inflammatory process. Inflammatory caspases 1, 4, 5, and 11(murine) form a crucial part of these inflammasomes and are required for the inflammatory process and play a defensive role in UTIs[21,22].

MATERIAL AND METHODS

In order to find studies examining the role of inflammatory caspases in urinary tract infections, a thorough literature review was conducted utilizing the PubMed and Scopus databases. Urinary tract infection, inflammatory caspases, and inflammasomes were the search terms we utilized. To get the most out of the literature, search phrases were utilized in every area, whether they were keywords or MeSH terms. Only English-language full-text publications that were accessible and published up until June 2024 were taken for review. Case reports, Chapters, commentary, and research unrelated to UTI, inflammatory caspases in UTI and inflammasomes in UTI were excluded. To find other papers that fitted our requirements, the reference lists of the chosen articles were also examined. This review covered every study that discussed inflammatory caspases in UTIs.

RESULT AND DISCUSSION

Pathogenesis during UTIs

Urinary tract infections (UTIs) begin when uropathogens contaminate, adhere, and colonize the urethra. Then, uropathogens migrate to the bladder with the help of pili and adhesins. Here, the host pathogen interaction will determine whether the pathogen will be eliminated or if the infection is successful. UPEC, *K. pneumoniae,* and *S. saprophyticus* cause uncomplicated UTI and can bind to bladder epithelia directly via uroplankin, á3â1 integrin, which acts as a receptor for UPEC and *K. pneumoniae*. *Proteus mirabilis, Pseudomonas aeruginosa*, and *Staphylococcus saprophyticus* are responsible for both uncomplicated and complicated UTI, and form biofilms. Gram-negative uropathogens express chaperone-usher

pathway (CUP) pili. It is a conserved family of adhesive fibers. CUP pili are made up of pilin subunits but do not contain complete immunoglobulin folds, whose final folding is achieved by donor strand complementation.

***E. coli* pathogenesis**

UPEC uses its virulence factor to facilitate bladder colonization to overcome innate and adaptive immune responses, which has been studied recently through various clinical isolates by meta transcriptomic and metagenomic studies in addition to in vivo, in vitro, animal, and human studies [1]. A deep molecular knowledge of the virulence factors used by UPEC has been achieved in these studies. UPEC can elicit symptomatic UTI through the use of virulence factors such as iron acquisition systems, SisA and SisB, lipopolysaccharides (LPS), á-hemolysin, type-1, and P-fimbriae[1]. To bypass the innate immune system and successfully colonize bladder epithelial cells, UPEC has adopted a range of strategies. Through regulation of NF-êB activity by genes involved in LPS biosynthesis or á-hemolysin, they can suppress the production of epithelial cells. It has been demonstrated that the UPEC strain CFT073 hinders TRIF and IL-6/IL-1 signalling cascades autonomously via MyD88 and TLR signalling by the virulence factor TcpC in a MyD88-dependent manner. Similarly, Uropathogenic *Escherichia coli* (UPEC) can penetrate bladder epithelial cells through adhesion mechanisms that rely on type-1 fimbriae. Following exocytosis, the majority of infiltrated UPEC is expelled back into the bladder cavity. UPEC that are not ejected from cells form intracellular bacterial communities (IBCs), which serve as internal reservoirs within the host cells. *E coli* genome contains 38 CUP pilus operons. One UPEC strain contained 12 different CUP pili[23]. While some have been identified in only a few strains of UPEC, others are seen in many strains. Various adhesins that bind to targets in the bladder or kidney epithelium cells are found linked to CUP pili. The four chaperone usher pathway pili in UTI infection are P-, F-17-, Fim-, and type 1 pili[24,25]. Adhesin Fim H is present on the tip of Type 1 pili. Invasion and colonization of umbrella cells in the bladder epithelia are initiated by type 1 pili. Here, Type 1 pili identified á3â1 integrin and mannosylated uroplankin. Once it binds to the cell, it initiates a signal cascade to activate the Rho GTPase that induces actin rearrangement and UPEC internalization, which helps uropathogens to evade host defense and make them resistant to prescribed therapy. Still, the bladder epithelium is shielded against UPEC invasion by the natural defensive clearance system. This mechanism requires TLR4 expression in uroepithelial cells[26]. LPS can also stimulate TLR4 and increase cAMP levels by inducing AC3 (Adenyl cyclase) that results in the exocytosis of vesicular UPEC. However, some UPEC can escape from this expulsion pathway and reach the cytoplasm to form transient intracellular bacterial communities (IBCs)[27]. When IBCs mature, some of them disperse and attack other cells, and the cycle repeats. IBCs help UPEC to survive in the urinary tract and to overcome the TLR4 mediated expulsions pathway, exfoliation of umbrella cells, etc. Presence of intracellular bacterial communities (IBCs) in human is verified in recent studies[28,29,30]. UPEC can also form quiescent intracellular reservoirs (QIRs) in transitional cells. QIRs contain non-replicating bacteria that remain in the quiescent phase for months and can be reactivated to initiate recurrent UTI. UPEC revival from QIR is proposed by a signal from new umbrella cells that form from the differentiation of immature cells underlying the uroepithelial cells. P-pili adhesin

Table 1. List of Receptor families having different Pathogen Recognition Receptors

Receptor Family	Acronym
Toll-like receptors	TLRs
C-type lectins	CTLs
Retinoic acid-inducible gene-I (RIG-I)-like receptors HIN-200	RLRs
Nucleotide binding and oligomerization domain (NOD)-like receptors	NLRs

Pap G binds to glycolipid-containing globoside in the human kidneys and blocks IgA transport into the urinary tract by interacting with TLR4. It stimulates an immune response to decrease the expression of polymeric immunoglobulin receptor (PIGR), thus inhibiting IgA transport. Thus, PapG modulates renal infection. Recent studies have shown that TNF signaling dynamics differ between initial acute cystitis and initial chronic cystitis, and this regulation of the dynamics of TNF signaling can provide insight into how an initial UTI infection can modulate susceptibility to UTI in humans in future infections[31]. Another virulence factor in UPEC is a pore-forming toxin, á-hemolysin (HlyA), which forms in response to periplasmic stress in UPEC during UTI infection by inducing a periplasmic cpxA (CpxR-CpxA) two-component signal transduction system) through the cpxR response regulator. HlyA causes the death of urothelial cells by inducing NLRP3 inflammasome through caspase 1 and caspase 4 activation[32].

Klebsiella pneumoniae

K. pneumoniae also utilizes type 1 pili for colonization and biofilm formation[33]. The FimH adhesin of *K. pneumoniae's* Type 1 pili is homologous to UPEC FimH; however, their binding specificities differ significantly. Methyl mannose inhibits the development of biofilms mediated by UPEC FimH whereas in *K. pneumoniae*, this inhibition is achieved by heptyl mannose[34]. The FimH adhesin of *K. pneumoniae* exhibits weaker adhesive properties compared to UPEC FimH but plays a crucial role as a virulence factor in *K. pneumoniae*-induced UTIs and CAUTIs. In addition to Type 1 pili, *K. pneumoniae* also encodes Type 3 pili, which mediate colonization, biofilm formation, and persistence in UTIs[34].

***Enterococcus* pathogenesis**

Enterococcus faecalis and *E. faecium* are gram-positive bacteria that cause CAUTI. It represents many adhesin factors, such as collagen adhesin Ace, Enterococcal surface protein (Esp), enterococcal polysaccharide antigen (Epa), endocarditis, and biofilm association pili (Ebp)[35]. Ebp is used for biofilm formation in CAUTI. Catheterization stimulates the inflammatory response to induce the release of fibrinogen into and deposition on the bladder. EbpA (Ebp pilus Adhesin) contain N -terminal fibrinogen binding domain that help in biofilm formation and colonization in CAUTI by *Enterococci*[36].

Proteus mirabilis

A variety of *Proteus* species use mannose-resistant CUP pili named (MR/P) pili that can infect the bladder and kidney and persist there by colonization and biofilm formation on the catheter[37]. *P. mirabilis*-like fimbriae (PMFs) is another CUP pili, which are crucial for colonization of the bladder and kidney, and non-agglutinating fimbriae (NAFs) attach to uroepithelial cells. We still don't know what PMFs, NAFs, and their receptors do in vivo. In addition to CUP pili, P. mirabilis hides two autotransporters: AipA (adhesion and invasion mediated by the Proteus

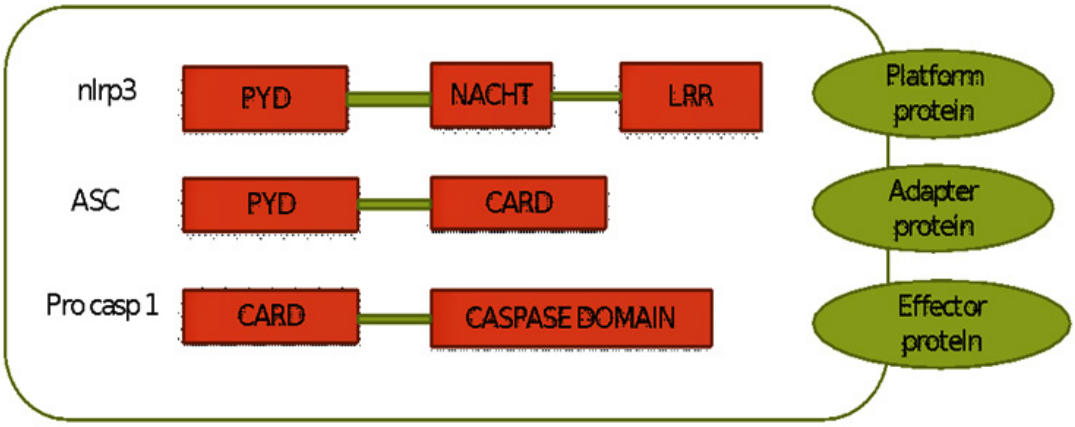

Fig. 1. Structure of NLRP3 Inflammasome, It consist of three domains named, C-terminal LRR, central NACHT and N-terminal NLRP3domain

autotransporter), which causes human bladder and kidney infections in vitro, and TaaP (trimeric autoagglutinin autotransporter of Proteus), which causes bladder infections[38]. UTIs affect millions of women worldwide annually. UTI in hospitalized patients, especially those with an indwelling urinary catheter, increases the cost and complexity of treatment. Patients suffering from symptomatic UTI are commonly treated with broad-spectrum antibiotics; however, enhancing antibiotic resistance affects the gut microbiota, which raises the need for alternative therapeutic approaches that can selectively treat UTIs. A detailed understanding of UTI pathogenesis is required to develop novel antimicrobial agents to treat UTIs.

Inflammatory caspases and inflammatory Response

Inflammatory Caspases

Endopeptidases are classified as caspases. These proteases undergo nucleophilic attack by cleaving substrates at the aspartic or glutamic acid residues using a catalytic dyad consisting of histidine and cysteine. Many caspases that are categorized as inflammatory (caspases-1, -4, and -5) or apoptotic (caspases-2, -3, -6, -7, -8, -9, and -10) are encoded in humans. Depending on their activation mechanism and domain structure, which determine their location in cell death signaling hierarchies, caspases are further split into initiator and effector classifications. Synthetic initiator caspases are inactive monomeric zymogens. In contrast, initiator caspases must cleave executioner caspases, which are expressed as preformed dimers, for activation. Caspases-1, -4, -5, and -11 are the initiator caspases triggered within the inflammasomes causing the lytic cell death and the production of inflammatory mediators, which in turn trigger both pathological and host-protective immune responses.

Inflammatory Response

Protein complex structures called inflammasomes stimulate an immune reaction by maturing and secreting proinflammatory mediators, such as IL-1â and IL-18, as well as by inducing pyroptosis. Pattern recognition receptors (PRRs) that detect pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) initiate inflammasome formation[39]. Different caspases, which are proteases present in the cytosol in a non-active pro-form and activated by autoproteolytic cleavage or other caspases, are activated when the inflammasome assembles[39,40]. Proinflammatory caspases such as caspase-1 and

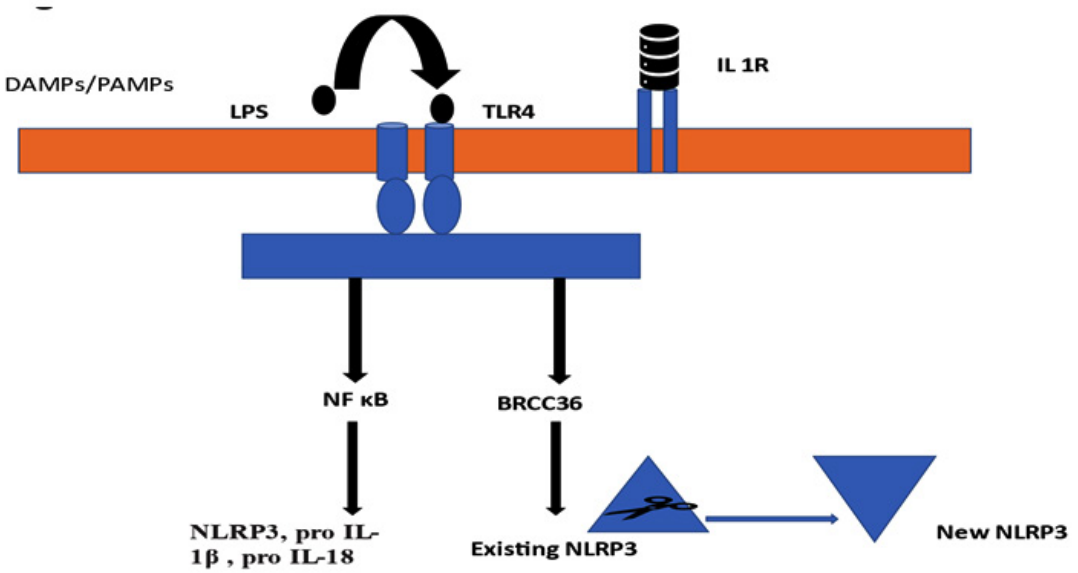

Fig. 2. Priming. Here LPS interact with TLR4 to start the process and it may also initiate on interaction with IL-1R receptor that further leads to generation of NLRP3 inflammasome and effector cytokinin via NFêB pathway. Existing NLRP3 is degraded through BRCC36 stimulation.

caspase-4 can cause pyroptosis in response to various stimuli. The pore-forming protein is cleaved and activated by proinflammatory caspases[39], and the combination of proinflammatory caspase activation and lactate dehydrogenase (LDH) release from dying cells is a useful indicator of pyroptosis. Caspases-1 transform pro-IL-1â into active IL-1â and facilitate the release of cytokines[39] during canonical inflammasome activation." Among inflammasomes, NACHT leucin-rich repeat PYD protein 3 (NLRP3) is the most well studied. Moreover, non-canonical inflammasome activation and pyroptosis are caused by separate gram-negative bacteria activating human caspase-4/-5 and its mouse homologue, caspase-11. ASC-dependent activation of caspase-1 and maturation of pro-IL-1â[41] have been demonstrated to be triggered by caspase-11 along with NLRP3. Independent of TLR4[41] cytosolic LPS receptors have been shown to activate non-canonical inflammasomes

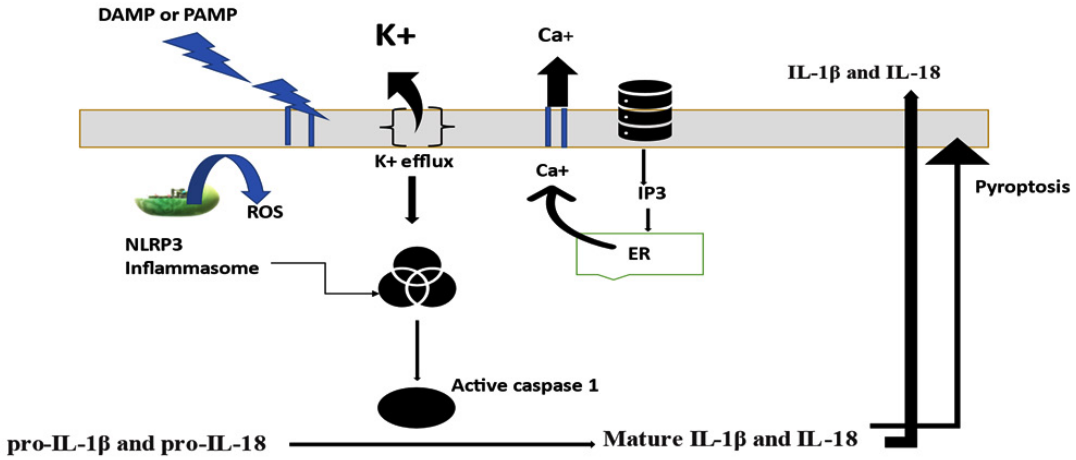

Fig. 3. Activation. DAMP and PAMP starts the activation with many changes like ROS production, Ca^{+} signalling and K^{+} efflux. Oligomerization of NLRP3 starts that leads to formation of ASC protein which further interact with procaspase 1. Procaspase 1 also form long filament from the ASC protein. After maturation it cleaves the pro IL-1â and pro IL-18 into their mature form. Mature caspase 1 cleave N terminal fragment of gasdermin D protein and pyroptosis initiates

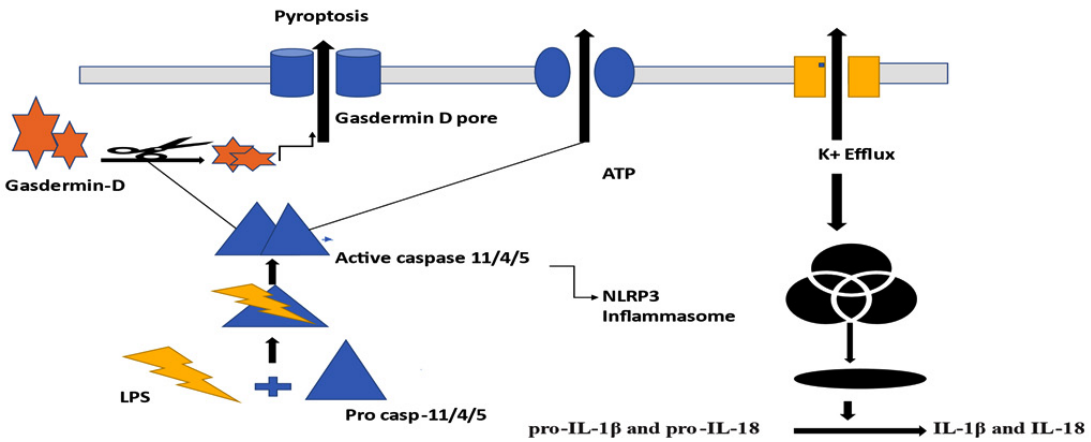

Fig. 4. Non Canonical Pathway. Here Caspase 11 interact with intracellular LPS , oligomerized, activates, cleaves the gasdermin D protein and initiates the pyroptosis. It is also associated in other events like ATP production, K^{+} efflux and NLRP3 formation.

through human caspase-4 and mouse caspase-11. It was recently discovered that caspase-4 binds to inflammasomes to cause pyroptosis and IL-1â release[41]. It is intriguing that caspase-4 is a cytosolic LPS receptor because it suggests a potential function for inflammasome-associated proteins in the bacterial implantation process. The ability of caspase-4 to detect UPEC LPS and control UPEC's intracellular perseverance of UPEC in bladder epithelial cells, for example, by pyroptosis, is currently unknown. It has been highlighted that a UPEC-mediated UTI is significantly influenced by the NLRP3 inflammasome. However, this information has been inconsistent. According to one study, UPEC-infected mice release IL-1â, and this IL-1â increased the intensity of infection. Mice deficient in IL-1â are shielded from contracting UTIs[42]. Nevertheless, some studies have noted that the immune response that prevents urinary tract colonization is boosted by UPEC-induced IL-1â[43]. Inflammasome-associated proteins have recently been shown to play a dual role as transcription regulators [44] and are essential for the release of IL-1â and IL-18. Currently, little is known about the roles of caspase-1, caspase-4, and NLRP3 in the release of additional inflammatory mediators from bladder epithelial cells during UPEC infection.

The pattern recognition receptors (PRR)

The initial hindrance to uropathogens comes in the form of urothelium epithelial cells, which provide a barrier to eliminate the infection and initiate activation of the innate defense structure. Pattern recognition receptors (PRR) are part of the innate defense structure that shields humans in cases of uropathogen attack in the urinary tract[45]. These receptors may be extracellular or intracellular in nature. Based on their location, the PRRs can be grouped into five families (Table1). Toll-like receptors and C-type lectin receptors are located on the membrane, whereas Rig-I-like receptor, AIM2 like receptor and nucleotide binding domains, and leucine-rich repeat-containing receptors identify pathogens intracellularly[46,47]. PAMPs are recognized by these cytosolic receptors, but they can also sense DAMPs released by the damaged and dying cells of the host. PRRs initiate a downstream signalling cascade to produce an inflammatory response upon interaction with a specific ligand, with the aim of expelling the pathogen.

NLP3 Inflammasome

NLRP3 is the most thoroughly studied inflammasome in the urinary pathology. It is composed of three separate domains (fig 1). The PYD domain enables protein-protein interactions through homotypic binding for subsequent signaling. The central nucleotide-binding domain, NACHT, initiates oligomerization. Autoregulation and ligand sensing are functions of the leucine-rich repeats (LRRs)[48,49,50]. The expression of various Nod-like receptors in the urothelium allows the urinary bladder to mount an immune response to uropathogens. These receptors include NLRP3, NLRP1, 6, 7, 12, NLRC4 (NLR with an amino-terminal CARD domain), and certain ALR family members. These NLRs and select ALRs serve as the key components of the inflammasome[51,52].

Role of caspase 1

Caspase 1 play an important role in the canonical inflammasome pathway. Priming and activation are the two steps in the canonical pathway. Canonical inflammasomes require three-component sensors, an adaptor, and an effector. By homotypic interactions of the death domains and the pyrin domain, these components assemble together. Sensor proteins (ALRs and NLRs) that bind to specific ligands undergo activation, oligomerization, and nucleation of the ASC (adaptor protein). ASC activates the effector protein procaspase-1. Pro-IL-1â and Pro-IL-18 produce mature cytokines when the effector protein caspase 1 cleave them via the inflammasome NLRP3 mechanism.

Priming

The first step is 'priming, ' which involves the accumulation of pro-IL-1â and pro-IL-18. Expression of inflammasome components starts off as ligand LPS (lipopolysaccharide) interacts with a non-NLR receptor TLR4, which shows that priming has been initiated (Fig 2). The nuclear factor kappa light chain enhancer of the activated B cell (NF-êB) pathway is responsible for the expression of these components[53] In priming pre-existing NLRP3 is also degraded by ubiquitination. The degradation of pre-existing NLRP3 acts as a licencing agent to activate the pathway[54].

Activation

Activation (Fig 3) starts when a DAMP or PAMP interacts with a purinergic receptor (purinergic receptors are categorised into P1and P2.

P1 acts as a receptor for adenosine, and P2 acts as a receptor for purine and pyrimidine nucleotide)[55]. This binding initiates many changes in the cell-like release of cardiolipin and mitochondrial DNA on the degradation of mitochondria, efflux of potassium, production of reactive oxygen species, lysosomal disruption with cathepsin release, and the translocation of NLRP3 in mitochondria. However, these switches do not occur with all kinds of ligands, so the required steps and stimulation in response to a particular ligand are yet to be explained properly. Oligomerization of NLRP3 begins in an activation step that initiates nucleation, which is a process of long filament formation of ASC proteins. Procaspase-1 also forms long filaments of ASC. The pro caspase 1 maturation starts when induced proximity is achieved by the interaction of procaspase 1 and ASC protein filaments. After the maturation of caspase, pro IL-1â and pro IL-18 into their mature forms. In contrast, the N-terminal fragment of Gasdermin D is cleaved by mature caspase 1[56], and pyroptosis is stimulated by this cleaved N-terminal fragment. Cells swell during pyroptosis and then rupture, releasing all the inflammatory content out of the cell, unlike apoptosis[57,58,59,60]. Both the processes have two common factors that caspase 8 and the Fas-Associated protein with Death Domain (FADD)[61,62]. Pyroptosis and maturation of IL-1â and IL-18 release both processes simultaneously after activation, but in specific situations. The inflammatory content released during pyroptosis includes ASC containing aggregates, high mobility group box1 and DAMPs such as uric acid and ATP. Neighbouring cells are also stimulated to activate the inflammasome pathway by these inflammatory components.

Caspase 4 and 5

Caspase 4/5 in humans and caspase 11 in mice play important roles in non-canonical inflammasomes[63,64,65]. The bacterial components of gram-negative bacteria, such as lipopolysaccharide (LPS), are accessed from the interior to the cytoplasm and then identified through caspase -4/-5/-11 via the noncanonical inflammasome. Previous studies suggest that Toll-like receptor TLR4 with myeloid differentiation MD2 and cluster of differentiation 14, that is, CD14, recognizes LPS[66]; however, these are not responsible[67,68]. Caspase-11/-4/-5 act as receptors for intracellular LPS.

Caspase 11

For optimum activation, caspase 11 binds to the lipid A moiety (hexa-acylated) of intracellular LPS through its CARD domain. The lipid A moiety (pentacylated) of LPS cannot strongly activate caspase 11[69]. Some pathogenic bacteria can evade the recognition by the immune system by changing the acylation state of LPS and also reduce the inflammatory response[53,70]. Some DAMPs released by damaged and dying cells can stimulate caspase 11 like oxidized phospholipid like intracellular LPS, but these oxidized phospholipids bind to different domain of caspase 11. These are also able to stimulate the production of IL-1â but are not able to stimulate pyroptosis[71]. TLR4-TRIF-Type-1 Interferon signalling (TIR-domain-containing adapter-inducing interferon-â-TRIF) stimulates the expression of caspase 11‘when LPS gets recognized by it. LPS recognition stimulates the TLR4_TRIF which further activates type 1 interferon via the IRF3 (Interferon regulatory factor 3). Type 1 interferon induces the expression of guanylate-binding proteins (GBPs), a family of interferon-inducible proteins[72]. Caspase 11 identifies the released products of the bacterial solubilized membrane that are solubilized by the interferon response gene B10, which is induced by GBPs[73].

Non canonical pathway

Caspase-4/-5 in humans is a duplication product of caspase 11[74]. Regular expression of caspase 4 is observed in human cells, but caspase 5 expression is intuitive in response to inflammation[75,48]. Type I and II interferon robustly stimulate the expression of caspase 5[66]. Caspases 4 and 5 can identify intracellular LPS and stimulate non-canonical inflammasomes. Studies have shown that both caspases are involved in a non-canonical inflammasome, but their ability to detect cytosolic LPS is still not clear. Therefore, it is assumed that caspases 4 and 5 work together in the non-canonical inflammasome[76]. The direct effector result of caspases -4,-5, and-11 is pyroptosis. Pyroptosis is achieved by pore formation upon binding and oligomerization of the N-terminal fragment of the gasdermin D protein to phospholipids present in the plasma membrane. This N-terminal fragment

of gasdermin D protein is cleaved by caspases 4/5/11[77,78,48]. Caspase -4/-5/-11 activation in the non-canonical inflammasome also activates the NLRP3 inflammasome[79]. This link is not clear, but recent studies state that caspase 1 activation in NLRP3 inflammasomes and the release of mature cytokines are also associated with gasdermin D cleavage mediated by caspase -4/-5/-11 during gram negative bacterial infection.

The urothelia possess the many PPRs that are able to form the inflammasome complex have PAMPs stating that they are evolved previously after interacting to infectious agents. UPEC possess PAMPs like LPS and flagellin that stimulate the NLRs. In urinary tract infections (UTIs) cytokines are detected early in urine that states the involvement of inflammasome. So, there is connection, but very few is known regarding role of inflammasome in defence system. NLRP1 is present in the urothelium and identifies muramyl dipeptide but no studies are found about the role of this NLRP1 in UTIs[78,48]. NLRP3, exist in the urothelium, and answer to hemolysin and LPS[79,80]. But there are diverse activators exist for NLRP3 which needs to study if they involved in innate defense against UTIs[80].

CONCLUSION

UTIs affect millions of people annually, posing a significant economic and clinical burden on society. Recurrence of UTIs is a major problem in the treatment of infections. The complexity of the treatment of patients also increases in cases of long stays in hospitalized conditions with indwelling catheters. It also places an extra burden on the patient. The first-line treatment administered to urinary tract patients is a broad-spectrum antibiotic, but the long-term use of these antibiotics results in the emergence of multidrug resistance (MDR) species of uropathogens and also alters the normal gastrointestinal microbiota of the patient. All of these complexities require the development of alternative treatment methodologies that can specifically and selectively treat infections. Therefore, a detailed understanding of the role of inflammatory caspases in the urinary tract infections pathogenesis of UTIs is crucial for us to be able discovering novel targets for the treatment of infections. This review explains how caspases 1, 11, and 4/5 are involved in the host response to uropathogens. Understanding their role in urinary tract infections will provide further insights into inflammation and will help to find a novel therapeutic approach to resolve the infection.

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Conflict of interest

The authors do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials**.**

Author Contributions

Nisha: Conceptualization, Methodology, Writing – Original Draft; Jinny Tomar: Supervision, Analysis, Writing – Review & Editing, Final Approval; Ravi Datta Sharma: Supervision, Analysis, Writing – Review & Editing, Final Approval; Deepak Chand Sharma: Supervision, Analysis.

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