

Innate Immune Response to Urinary Tract Infections Involving *Escherichia coli*

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Abstract

The innate immune system responds in a rapid, initially nonspecific manner to infection in the urinary tract. There are many molecules and cells involved in this response. These include: antimicrobial peptides, toll-like receptors, chemokines, cytokines, and neutrophils. The most common cause of urinary tract infections (UTIs) are uropathogenic *Escherichia coli* (UPEC). The innate immune system responds to the presence of flagella, fimbriae, and the lipopolysaccharide outer membrane of these bacteria. Antimicrobial peptides are used to lyse the bacteria and also prevent the bacteria from binding to epithelial cells in the urinary tract. The toll-like receptors sense the presence of the bacteria and signal for the production of molecules that cause immune and inflammation responses. The various chemokines and cytokines such as CXCL8, CCL2, interleukins (IL-6, IL-8, IL-10, IL-17A), and granulocyte colony stimulating factor (G-CSF), are used for much of the signaling in innate immunity. In addition, neutrophils play a major role in rapid removal of invading bacteria. The rapid innate immune response is designed to remove most of the bacteria within 24 hours in an uncomplicated UTI. This review presents an overview of the innate immune response to UTIs caused by UPEC and the host molecules and cells involved.

Keywords: Innate immunity; Urinary tract infection; *Escherichia coli*

Introduction

The immune system has two divisions, innate immunity and adaptive (acquired) immunity. There are some major differences between the two divisions but they share some cell functions and components. Innate immunity produces more rapid, nonspecific responses while adaptive immune responses are specific and often delayed. The innate immune system is the first responder to invading microorganisms, and the adaptive immune system will respond usually only after signaling from the innate system. The main parts of the innate immune system are: the natural barriers (skin, mucous membranes, etc.), nonspecific cells (phagocytes, natural killer cells, etc.), and nonspecific molecules (complement, interferons, etc.). In addition, many factors, such as age, general health, nutrition, and genetic makeup of any human host, affect how the immune system responds to microorganisms.

The urinary tract contains the urethra, urinary bladder, ureters, and kidneys. A main barrier defense in the urinary tract is the tightly joined epithelial lining of these components. In addition, there is continual flushing of the tract by acidic sterile urine. This continual flushing keeps microorganisms from being able to contact and adhere to the epithelial lining of the urinary tract. The innate immune system also has many components that work together to fight off potential infection. An uncomplicated urinary tract infection begins with the bacteria ascending up the urethra to the urinary bladder (cystitis). In more severe or complicated infections, the bacteria may continue ascending into the kidneys (nephritis).

Urinary tract infections (UTIs) have a huge impact on the healthcare industry. UTIs are more common in women. An estimated

1 out of 3 women will have experience a UTI before the age of 24, and UTIs result in an estimated 7-8 million healthcare visits per year in the United States [1]. The healthcare costs from UTIs in the U.S. is estimated to be over 2.3 billion dollars per year [2].

Virulence Factor	Function
Capsule	Antiphagocytic, evasion of immune recognition
Type 1 fimbriae	Adhesion
P fimbriae	Adhesion
Other fimbriae (S, F1C)	Adhesion
Flagella	Motility
Lipopolysaccharide	Endotoxic
Outer membrane proteins (e.g. OmpA, IroN, FhuA, IutA)	Receptors and membrane transporters
α-hemolysin	Hemolysis
Cytolysins (CNF1, CDT)	Cytotoxicity
Secreted autotransporter toxin	Cytotoxicity
Siderophores (aerobactin, enterobactin)	Iron scavenging

Table 1: Common Virulence Factors of Uropathogenic *Escherichia coli*

By far the most common cause (~80%) of UTIs is the gram negative bacteria *Escherichia coli*. The specific strains that usually cause UTIs are the uropathogenic *E. coli* (UPEC). These bacteria possess virulence

factors that are common to all gram negatives, such as the toxin A moiety of the lipopolysaccharide (LPS) outer membrane, factors common to all *E. coli* strains, plus specialized factors such as the P fimbria (pili). Table 1 lists the common virulence factors of UPEC strains.

In order for UPEC strains to cause disease (disease state varies with strains and whether the infection is uncomplicated or complicated) they have to be able to contact, adhere to, and invade the host cells; successfully compete for iron and other nutrients; and resist the innate immune defenses. UPEC initially adhere to the uroepithelial cells via P- or Type 1 fimbriae. The Type 1 fimbriae (via the FimH adhesin) also enable bacterial invasion of the superficial uroepithelial cells where the bacteria replicate and form intracellular bacterial communities (IBCs). This invasion by the bacteria can occur as early as the first 1-3 hours of infection. There is intermittent shedding of the bacteria out of these cells into the lumen of the bladder, and the bacteria inside the cells are shielded from the host's immune system and antimicrobial agents [3,4].

Innate Immune Defenses to UTIs

Innate immune response can be mediated by intrinsic or extrinsic stimulation. Extrinsic stimulation is mediated by host cell receptors (cells don't have to be infected). Intrinsic stimulation is mediated by intracellular signals in infected host cells [5]. Initial binding of the bacteria to host uroepithelial cells results in the production of inflammatory mediators including increased interleukin-6 (IL-6) and interleukin-8 (IL-8), and initiating apoptotic cascades in the epithelial cells leading to exfoliation of the superficial epithelial cells. Recognition of bacteria LPS via Toll-like receptor 4 (TLR4) results in recruitment of neutrophils to phagocytose the bacteria [6,7]. Major players in innate immunity defense include antimicrobial peptides (AMPs), toll-like receptors (TLRs), and innate immune cells; as well as other effectors and immune mechanisms.

Antimicrobial Peptides

When *E. coli* are present in the urinary tract, they are motile via flagella. Before these bacteria can attach to the host cells, they may be bound by certain antimicrobial peptides (AMPs) produced by phagocytic leukocytes and epithelial cells. These AMPs, such as uromodulin, defensins, cathelicidin (LL-37), lactoferrin, hepcidin, and ribonucleases 6 and 7, are the immune system's front line attempt to keep the bacteria from being able to bind to the cells. The epithelial cells will rapidly secrete AMPs when the presence of bacteria are sensed [8,9]. Many AMPs have bacteriocidal activity that is due to their distinct structure and charge which result in bacterial cell membrane disruption [10].

Uromodulin (Tamm-Horsfall protein), which is produced in renal tubular cells, has been found to have multiple functions including defensive roles against infection by binding to the type 1 fimbriae on *Escherichia coli* to prevent the adherence of these bacteria to uroplakin receptors [11]; binding to IgG, complement 1q, and tumor necrosis factor; and acting as a chemoattractant and proinflammatory molecule [12]. Uromodulin also activates myeloid dendritic cells (DC) via TLR4 which results in activation of NF- κ B [13].

Defensins in humans are classified into two families: α -defensins, and β -defensins. The α -defensins (also known as human neutrophil peptides - HPNs) are found in the primary granules of neutrophils, and can be secreted to the cell's surface. HPNs encounter bacteria

either when the phagocytic vacuole fuses with the HPN, or after being secreted. The HPNs provide non-oxidative antimicrobial activity [14]. The β -defensins are expressed constitutively in epithelial cells. Human β -defensin-1 (HBD-1) has been found to be widely distributed in areas of the body with mucosal epithelium; and for the urinary tract more specifically, in the collecting ducts, distal tubules, and loops of Henle, where they may inhibit attachment of bacteria to the epithelial cells [8]. HBD-1 may also act as a chemoattractant for some T lymphocytes and immature dendritic cells (interact with CCR6 receptor) [8,9,15].

Cathelicidin is stored in neutrophil granules and may be produced by epithelial cells, monocytes, and T cells. Cathelicidin also fuses with the phagosome and acts by forming holes in microbial cell membranes. Cathelicidin also participates in recruitment of leukocytes with a resulting increased expression of chemokines, such as CXCL8 and CCL2, and their receptors. This affects recruitment of phagocytes, monocytes, immature dendritic cells, and T cells (interacts with fMLP-receptors). In addition, cathelicidin is responsible for release of proinflammatory molecules such as histamine and prostaglandins by degranulation of mast cells [8,9,15].

Lactoferrin is stored in granules of neutrophils and has two antimicrobial effects. It is an iron-binding molecule that can sequester the iron, making the iron unavailable to bacteria. This iron sequestration also seems to affect the ability of the bacteria to form biofilms. Lactoferrin has also been shown to have a direct antimicrobial activity. It is able to bind to bacterial LPS causing the LPS to be released, which damages the bacterial cell membrane. Because substantial amounts of lactoferrin could be detected in the urine of people with UTIs, it was proposed as a biomarker that could be rapidly detected, and therefore useful for diagnosis of UTIs [16,17].

Hepcidin is synthesized primarily in the liver and excreted through the kidneys. Hepcidin production is induced during inflammation by IL-6 (hepcidin is a type-II acute-phase protein). It plays a dual role in bacterial infections: it inhibits the amount of available iron, and it is able to bind and permeate the cell membranes of microorganisms (the structure of hepcidin is similar to the defensin family). The ability to inhibit iron production occurs through the binding to and degradation of the iron exporter ferroportin. This blocks macrophages and other cells that may sequester iron during infection from releasing iron [18,19].

Ribonucleases (RNases) 6 and 7 are members of the RNase A superfamily. RNase 7 is constitutively produced at high levels (compared to other AMPs) from the uroepithelium. It has a broad spectrum antimicrobial activity involving permeation and disruption of the bacterial cell membrane. RNase 7 increase with infection, and it has been shown to rapidly clear uropathogens (within 60 minutes). RNase 6 is produced by monocytes and neutrophils, and is not constitutively expressed, but is induced by infection. It is seen as early as 30 minutes after infection starts, and levels increase over time. Antimicrobial activity of RNase 6 is the same as RNase 7 [20,21].

Toll-Like Receptors

Toll-like receptors (TLRs) are a family of transmembrane proteins that are sensors for pathogen-associated molecular patterns (PAMPs). UPEC in the urinary tract are detected via TLR4 or TLR5, which can be found on epithelial, monocytes (and macrophages) and immature dendritic cells. TLR4 responds to binding by bacterial LPS (to CD14 in association with TLR4) or fimbriae (P fimbriae binding to glycosphingolipids associated with TLR4; type 1 fimbriae binding to

mannosylated glycoproteins on uroplakins or cell membranes in association with TLR4). TLR5 responds to binding by bacterial flagella (flagellin). When TLR4 and TLR5 are bound by ligand they are phosphorylated on the cytoplasmic domain. Activation of the TLRs initiates signaling of immune and inflammation responses [22-26]. TLR4 activation by LPS or P fimbriae binding results in secretion of IL-6 and IL-8. The signaling response from TLR-4 binding LPS may occur through two separate pathways; by activation of NF- κ B, or a more rapid response initiated by an increase in intracellular Ca²⁺. Both pathways result in secretion of IL-6 [27]. The binding of LPS to CD14 is facilitated by an acute-phase protein, the lipopolysaccharide-binding protein (LBP). LBP binds to the LPS on the bacterial and is responsible for the monomerization of the LPS. The LBP then catalyzes the transfer of the LPS to CD14 [28,29].

Bladder Epithelial Cell Exfoliation

One of the defenses of the urinary bladder is rapid exfoliation of epithelial cells in response to bacterial type 1 fimbriae binding to uroplakin. Binding causes the uroplakin to be phosphorylated on its cytoplasmic tail. This sets off a signaling cascade that rapidly increases the intracellular calcium and initiates cell apoptosis. This rapid exfoliation is an attempt to prevent the bacteria from being able to invade the bladder cells; and in conjunction with other immune effectors, is responsible for the initial rapid clearance of bacteria. It is also an effective way to disrupt the IBCs in those cells [30,31].

Other Receptors

Epithelial cell death in the urinary bladder releases large amounts of ATP which is used as a danger signal. The ATP binds to, and activates, G-protein coupled P2Y receptors found on the uroepithelial cells. This binding and activation induces production of interleukin-8 (IL-8) by the uroepithelial cells. Binding of IL-8, plus binding of ATP to P2Y receptors on the neutrophils is required for chemotaxis of the neutrophils [32-34].

Another receptor that has a function in UTIs is the erythropoietin receptor (EPOR). This receptor functions as a homodimer with high affinity for erythropoietin (EPO) on erythroid progenitor cells [35]. During an innate immune response EPO is released in response to tissue damage (and cell death) and binds to a heterodimeric receptor composed of an EPOR subunit and a CD131 subunit. This composite receptor has a much lower level of affinity for EPO and then a much larger amount of EPO needs to be present. EPO in this context has an anti-inflammatory effect and prevents programmed cell death [36,37].

Cytokines and Other Effectors

During the early innate response to UTIs there are a number of pro-inflammatory molecules produced, as well as molecules produced and released in response to inflammation. These include the cytokines IL-6, IL-17A, and lipocalin 2. In addition, granulocyte chemotactic molecules are produced; such as the cytokine IL-8 and granulocyte colony stimulating factor (G-CSF). IL-10 also is produced and has multiple roles [38,39].

IL-6 has multiple functions, and is responsible for signaling that results in production of acute-phase proteins [40], such as serum amyloid A, ceruloplasmin, and complement. Serum amyloid A functions as a chemoattractant for immune cells, such as monocytes, neutrophils, and T lymphocytes [41]. Ceruloplasmin is able to oxidize

iron which makes it difficult for the UPEC to uptake any iron [42]. Complement components functions in opsonization of microorganisms and produce pores in the outer membrane of the bacteria causing leaking of cell contents [43,44]. IL-6 may activate B cells resulting in production of secretory IgA (sIgA) and stimulation of production of C-reactive protein, which further encourages the inflammatory cascade [14].

IL-17A functions in attracting neutrophils indirectly. IL-17A acts in conjunction with tumor necrosis factor-alpha (TNF- α) to stabilize the mRNA of IL-6 and IL-8 [45-47].

IL-8, which is produced by a variety of cells (e.g. monocytes, uroepithelial cells) in response to LPS and other factors, functions as a chemoattractant and activator of neutrophils (via CXCR1 and CXCR2 receptors), and promotes transepithelial infiltration of these cells [48,49]. Binding of IL-8 to either CXCR1 or CXCR2 on neutrophils mediates release of granular enzymes and mobilization of intracellular Ca²⁺. The respiratory burst is mediated only through CXCR1 stimulation [50].

G-CSF functions to recruit neutrophils. G-CSF induces the immature progenitor cell to leave the bone marrow. These cells then enter the bloodstream and mature. The mature neutrophils then respond to signals from G-CSF (and other molecules) and travel to the site of infection; in this instance, the bladder [51,52].

IL-10 is primarily produced by monocytes early in UTIs. This production is probably induced by recognition of LPS. IL-10 has been characterized as a regulator of the innate immune response, having multiple upregulatory and downregulatory immune functions. In UTIs, the main function may be to protect the host from exaggerated immune responses which produce inflammation and tissue injury [53-55].

Lipocalin 2 is an antimicrobial molecule that is produced by epithelial cells and neutrophils, and stored in neutrophil granules. It is released from uroepithelial cells which are stimulated by TLR4 binding, and released from neutrophil granules in response to inflammation. It acts by binding the siderophore enterobactin of *E. coli*, thereby inhibiting the ability of the bacteria for scavenging iron [56,57].

Innate Immune Cells

The main effector cells of innate immunity in UTIs are neutrophils. They are induced to travel, as immature cells, out of the bone marrow and into the bloodstream; and as mature cells, to travel out of the bloodstream to the uroepithelial layer, and then into the lumen of the bladder or tubules, wherever the bacteria are located. There are multiple factors (see previous paragraphs) that are involved in the recruitment of neutrophils. In uncomplicated UTIs the main function of neutrophils is to phagocytose and kill bacteria. In more severe infections other functions of the neutrophils become important.

In addition to phagocytosis, neutrophils function by secreting many types of signaling molecules (cytokines, chemokines, etc.). Initially, the signaling is for recruitment of additional neutrophils. As an infection progresses, or becomes complicated, neutrophils recruit monocytes and macrophages, and recruit and activate dendritic cells [58-60]. The macrophages also function in phagocytosis and produce proinflammatory cytokines and additional toxic metabolites [61]. Dendritic cells acting as antigen-presenting cells are a primary inducer of adaptive immunity. Dendritic cells may also function in innate

immune regulation [61,62]. Neutrophils may additionally function as a bridge to adaptive immunity by acting as antigen-presenting cells [63].

Concluding Remarks

The early, rapid responses caused by binding and signaling of AMPs and TLRs, etc., are designed to be lethal to the microbial invaders. This rapid response kills many of the bacteria within the first 2 hours, so that in a healthy individual or the person with an uncomplicated UTI, all or most of the bacteria will be dead within 24 hours, and completely eliminated within a few days [22]. In addition to direct killing activities, the cells of the uroepithelium and immune system produce molecules that inhibit the ability of the bacteria to attach to host cells and obtain iron, which severely limits their pathogenesis. In chronic, or complicated UTIs the effects of the innate immune response often cause far more damage to the host than do the bacteria. When bacteria are present for an extended time (and invade the tissues), the adaptive immune system is brought fully into play.

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