The innate immune response during acute urinary tract infections; an overview

Review Article

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Abstract:

The components of immune system are specific (adaptive immunity) and non-specific (innate immunity). Regardless of antigenic properties, the non-specific components function either as eliminators or barriers of wide range of pathogens. A person is born with innate immunity as the natural resistances, which has three kinds; anatomic mechanical and biochemical factors. The resistances are provided by innate immunity via various chemical, cellular and physical approaches. The colonization, entry and spread of microorganisms can be prevented by innate immunity. Two main sub-divided types of adaptive immunity are humeral and cellular. Active immunity resulting from the development of antibodies in response to the presence of an antigen is a long-term and acquired immunity. This review article summarizes some important potential mechanisms in innate immune system. The host renal tract which has been investigated from many aspects of the pathogenesis of urinary tract infection (UTI) are still poorly defined and require a better understanding of the pathophysiology immune system.

Keywords: Adaptive immunity, Antibiotics, Children, Innate immunity, Urinary tract infection

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Introduction:

Immunity has two non-specific (innate immunity) and specific (adaptive immunity) components [1-3]. A person is born with innate immunity as the natural resistances. The resistances are provided by innate immunity via various chemical, cellular and physical approaches. The colonization, entry and spread of microorganisms can be prevented by innate immunity [1, 4]. Two main sub-divided types of adaptive immunity are humeral and cellular. Naturally acquired immunity develops via non-deliberate contact with a disease causing agent, while artificially acquired immunity occurs just through deliberate measures like vaccination [5-8]. Acquired passive immunity which is short lived can occur through transfer of activated T-cells or antibodies from an immune host whereas active immunity is a form of long-term and acquired immunity resulting from the development of antibodies in response to the antigen presence [3, 4, 6, 9]. The urinary tract is a sterile system under the normal circumstances. By age 6, 1%–2% of males and 3–7% of females suffer from a urinary tract infection (UTI). Long-term complications of UTI are scare, hypertension and chronic renal disease. Thus, it is necessary to find a greater understanding of UTI pathogenesis and how the body protects urinary tract and kidney from microbial pathogen [6, 10].

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The nature of this human immune is unknown. The human defense mechanisms include numerous components of the immune system as well as genetic background and environmental exposures can change each component [6, 8].

The aim of this study was to describe human defense mechanisms in children, to pay more attention to the studies whose quality is not adequate in the field of UTI in Iranian and global children and to focus on the need of research in this area. This review article focused on how the innate immune response keeps urinary tract sterility and discussed about the recent advances in the understanding of how this pathogen interacts with the host.

Innate Immunity versus Adaptive Immunity in Urinary System

Innate immune is composed of proteins and antimicrobial peptides (AMP) which speedily neutralize the chemokines, invader and cytokines that attract phagocytes to a threatened site as well as increase their microbicidal capacity and the phagocytes themselves [6, 11, 12]. The bacteria may remain in the urinary tract system in spite of the innate immune response. Hence, a more specific adaptive immune response including cellular and humoral responses is resulted [1, 5, 6].

Phagocytic cells as a first line of defense are belonged to polymorphonuclear leukocytes (PMNs; neutrophils) and derived from the bloodstream directly to the site of bacterial invasion [10]. Uropathogenic Escherichia coli (UPEC) is the causative agent for 85–95% of community suffered from UTI and 50% of all patients with nosocomial infection in hospital [3, 13]. Most E.coli resulting in UTI pertain to O (Cell wall), K (capsular) and H (flagella) serotypes [14, 15].

A recurrence of infection occurs in 10-30% of children with UTI, and most of these recurrences happen during 12 months of the primary infection [5, 11, 15]. It may be that both bacterial factors and human host help the occurrence of UTI. Human immune system is categorized into acquired host factors and natural host defense factors. In the balance between infection of the urinary tract and sterility, host factors play a key role [12].

Features likely to contribute to disease of the human immune system involve the responses to antigens (B- and T-cell features, PMNs), efficiency of bacterial destruction (e.g., lysozyme, complement) and types of antimicrobial substances produced (e.g, immunoglobulins, Cytokines) [16].

Adhesion of bacteria to epithelia lining the urinary tract can be prevented by release of constitutive and inducible bactericidal antimicrobial peptides such as alpha- and beta-defensins and cathelicidin, lactoferrin, Tamm-Horsfall protein and lipocalin. Cytokines (IL-1 and TNF alpha) and chemokines (IL-8) activate and attract large numbers of macrophages and neutrophils which damage tubulointerstitial parenchyma with persistence of growing numbers of microorganisms [16-19].

Biochemical and anatomical defense consists of paraurethral glandular secretion urine stream, IgA secretory, urine inhibitors (PH, Osmolality and Urea) and bladder emptying [16]. Bacterial survival is decreased within the urinary tract via the presence of salts and urea, low pH, distance barrier of male urethra, other toxic metabolic end products, mucus in urine and hypertonic nature of kidney medulla [18].

Mechanical Factors

It seems that there are many mechanical forces to reduce UTIs, containing flushing mechanism and epithelial cell sloughing, urine flow and voiding, epithelial shedding as well as mucus shedding. A robust innate immune response is produced as uropathogenic E. coli prevails the mentioned physical barriers through adhering to the epithelium [10, 15]. The papillary configuration is another factor which controls the renal susceptibility to scarring when the ducts of the papillae open to the calyces. A convex papilla has no reflux since the slitlike or crescentic openings of its collecting ducts obliquely open on the papilla, while a flat papilla or concave/compound papilla has reflux for the collecting ducts open at right angles onto a flat papilla [16, 17].

Tamm-Horsfall glycoprotein (THP)

Moreover, THP which is a glycoprotein (mucoprotein) and exists in urine is known as uromodulin or uromucoid and in humans is encoded by the UMOD gene [4]. THP is not produced from blood plasma whereas is generated from the epithelial cells in the thick ascending limb of the distal convoluted tubules, collecting ducts of mammalian kidney and loop of Henle [4, 11, 15].

Although the role of THP is not well cleared, THP can really participate in transporter function and have a role in regulatory physiology. THP, itself, is not antimicrobial, stimulates the bacterial adherence and is the matrix of casts from the secretion of renal tubular [3, 19, 20]. Antibodies to THP have been observed in different forms

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of nephritis (e.g. Balkan nephropathy, Bence Jones proteinuria) [21-24].

Defensins

Defensins constrained by three sets of disulfide bonds are a group of highly structured compact peptides and highly cationic antimicrobial peptides produced by some variety of mammalian cells. The α and β classes are different based on the manner of folding. After exposure to pathogens, defensins which have the capacity to kill them are produced [9, 25]. The α- and β-defensins which attract immature dendritic cells are categorized based on chromosome 8p23.1. The α-defensins, Human neutrophil peptides1 (HNP1) to HNP4, exist in high concentrations of neutrophils and supply the neutrophil with its microbicidal and nonoxidative activity. The β-defensins are extensively expressed through the epithelia [26-27]. The strongest evidence is that in fact the defensins play the important role in the defense of the kidney of a genetically-engineered mouse whose defensin gene which is similar to the constitutively expressed Human β-defensin 1 peptide (HBD1) has been eliminated [27, 29].

Lactoferrin

Lactoferrin is a sub-fraction of whey protein, single-chain glycoprotein, the first line of defense for the body's immune system, present in the body's secretions such as mucus, milk, blood, saliva and tears as well as binds easily with iron [18]. Lactoferrin correlated with the luminal surface is expressed in the distal collecting tubules. A study has represented that the lactoferrin has beneficial effect on gut health and helps to prevent from viral and bacterial infections and cancers [30].

Cathelicidin

Cathelicidin as a linear peptide is expressed by circulating white cells on all epithelial surfaces. It is expressed along the human urinary tract [18, 31]. Cathelicidin is a gene dependent on vitamin D, and vitamin D stores can affect susceptibility to UTI in selected individuals. Vitamin D supplementation may be effective to prevent from UTI [6, 12].

Antimicrobial Peptides (AMPs)

AMPs are extensively spread in the nature and have been found in specific fungi, bacteria, plants, protozoa and multicellular animals [6]. Up to now, almost 1000 various naturally occurring peptides have been detected. Generally, AMPs are tiny, between 20-60 amino acids and positively charged due to the presence of amphipathic and lysine and/or arginine residues. All epithelial cells which come in contact with microorganisms produce AMPs [15, 31].

Lipocalin

Iron-trafficking protein removes or delivers iron from the cell. Lipocalin has multiple processes such as innate immunity, apoptosis and renal development. Lipocalin plays a role in innate immunity, possibly by sequestrating iron that limits bacterial growth [3]. The certain stimuli, directly responsible for the induction of lipocalin, have not been known, yet. Lipocalin prepares a rapidly protective, antimicrobial and responsive function, limiting the invasion by uropathogens during the subsequent stages of recovery [32].

P blood group secretor status

P fimbrial attachment of bacteria to the urothelium only happens through glycolipid epithelial cell receptors which are members of the P blood group consisting of several antigens, Pk, P and P1. A decreased incidence of bacterial adherence to the urothelium can be found if the P blood group is secreted [33].

Toll-Like Receptors (TLRs)

TLR families are pathogen recognition and immune system. TLRs are the pattern recognition receptors expressed on epithelial cells and leucocytes, and recognize the preserved molecular motifs on pathogens and activation of the immune system [3]. So far, thirteen human (TLR1-TLR13) and nine murine TLR proteins associated with the original Drosophila Toll gene have been discovered [18, 26]. The activation of TLRs via different types of ligands induces the inflammatory chemokines and cytokines. For immune mobilization and UPEC recognition, TLRs 2, 4, 5 and 9 are very important. It has been indicated that the TLR2 responds to the components of Gram positive bacteria [34].

The major lipopolysaccharide (LPS) sensor in mammals known as TLR4 is possibly recruited as part of the innate immune defense at this phase. TLR4 exists on the luminal surface of bladder epithelium [18, 35, 36] which generates cytokines, firstly via the stimulation of host TLR4 by bacterial LPS, that recruit PMNs to help to remove the bacteria [37]. The production of cytokines generated through bladder epithelial cells is actively suppress the UPEC. Moreover, a safe haven for UPEC evasion from infiltrating PMNs is provided by the intracellular niche. The colonization with UPEC is

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decreased by bactofection with TLR4 in the kidney and bladder by 91% and 41%, respectively [11, 38].

Complement activation

Complement is a system of interacting proteins as the heat-labile complementary principle and about 15% of the globulin fraction of serum. Age can affect the normal concentrations of serum complement components [39]. The complement system as an essential component of innate immunity is widely conceived as the lectin, alternative and classical pathways which depend on and interact with each other for their full activity. The activation of each pathway results in formation of C3 and C5 convertases and the generation of biologically active components includes opsonins, membrane attack complex (MAC) and anaphylatoxins [40].

Mannosylated uroplakin proteins

Mannosylated uroplakin proteins serve as the receptors for invasion and binding to UPEC at the tips of type 1 pili by the FimH adhesin and coat the surface of the superficial umbrella cells of the bladder. The serious infection risk appears quite variable in humans. During bladder contraction, the reversible adjustments of the area of apical urothelial surface are influenced by the plaques retracted into the cytoplasm [41]. Their reinsertion from unique cytoplasmic organelles named fusiform vesicles during bladder distention deliver preassembled crystalline arrays of uroplakin proteins to the surface of apical cell. Adhesion of bacteria to epithelia lining the urinary tract can be prevented by release of constitutive and inducible bactericidal antimicrobial peptides such as α- and β-defensins and cathelicidin, lactoferrin, Tamm-Horsfall protein and lipocalin. Microorganisms which overcome these early defenses activate an innate immune response and contact uroepithelia via TLR [1,12, 31].

Bacterial factors

Attachment

Attachment between the bacteria and uroepithelial cell via factors such as type 1, P pili and fimbriae is considered as the initial and important event in infection. Voiding cannot delete the bacteria attached to the upper urinary tract. These adhesions mediate the interactions which can also stimulate a number of host responses that can directly affect the outcome of a UTI. Exfoliation of the superficial umbrella cells happens at the last stages of the acute infection in an attempt to omit the bacterial burden [4,19, 42].

Invasion

Intracellular bacterial communities are formed after the bacteria insert to the bladder epithelial cells and interact with uroplakins and lipid rafts [4]. When these communities develop, they make cellular pods which protrude from the surface and might detach. Traditionally, UPEC has not been implicated as an intracellular pathogen. More lately, several adhesive organelles by UPEC with a few host factors have directly modulated and/or triggered the bacterial entry into the host cells. Especially, both Dr family adhesins and type 1 pili are considered as factors which are able to effectively progress the bacterial invasion of host cells through activating the distinct host cell signaling events.

Fimbriae or pili have a critical role in sex and conjugation of organism and may enhance the uropathogenicity. Fimbriae are hair-like originate and very thin, and are found in the cytoplasm of the cell. Fimbriae project via the cell wall and membrane. Bacterial adherence to red blood and uroepithelial cells is mediated by the bacterial fimbriae. The Gal 1-4 Gal oligosaccharide fraction is considered as the specific receptor. Totally, 76-94% of pyelonephritogenic strains of E. coli compared with 19-23% of cystitis strains have P fimbriae [42]. More than 80% of all UPEC produce type 1 fimbriae (virulence factor) which are responsible for elevating the inflammatory response correlated to the bacterial invasion and adhesion in UTI [42]. This family of adhesins is generally faced with the sever virulence factor [2, 43].

Siderophores

The organisms which apply the urinary tract as “fertile soil,” usually the gram-negative microorganisms' common to the distal bowel, need sufficient iron concentrations to support the growth. The organisms produce organic iron scavengers named siderophores which are empty as secreted and are pronely recovered as loaded with iron to remove their nutritional need of iron. Microorganisms resulting in UTIs have modified this iron-capture system in such a way that notify us of the antimicrobial defenses which are built around the iron economy [44, 45, 46]

Iron is a necessary nutrient for bacterial viability within the host, and the UPEC illustrates multiple mechanisms for iron extraction so that the most common of them is heme uptake and siderophore receptor systems. The siderophore systems are composed of aerobactin and entrobactin along with receptors including Iha, IreA and IroN [47].

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Haemolysins

Two common types of this toxin (haemolysin) are α-haemolysin and β-haemolysin. The former is a heat-labile extracellular protein lyses erythrocytes and its production may be chromosomally characterized or plasmid. The latter (β-haemolysin) is a cell related to the haemolysin with a similar range of haemolytic activity just as α-haemolysin [48, 49].

Cytotoxic necrotizing factor (CNF)

A subfamily of small GTP binding proteins is CNF types 1 and 2 which contribute to virulence and regulate the actin cytoskeleton. Membrane ruffling which forms the focal adhesions is shown by eukaryotic cells exposed to CNF1 [50].

Protectins

The UPEC expresses a covering of polysaccharide capsule. The polysaccharide, especially LPS, plays a pivotal role in virulence [51].

Normally, the urine is sterile and the defensive characteristics of uroepithelia aid to preserve this sterility as strategically need to survive for long-term. The serious infection risk appears quite variable in humans [19, 52, 53].

Although there are numerous host defenses, most patients end up having recurrent UTI. New studies have suggested that the uropathogens may attack the surfaces of epithelial cells and replicate as well as this invasion can cause the superficial cells to exfoliate [51].

A common bacterial infection is UTI in children [55]. This infection is recurred in more than 30% of children with UTI, and most of these recurrences happen within 12-18 months of the primary infection. The risk factors are genetic and other factors. Though there are many progresses in the interaction between host renal tract and pathogenic bacteria, numerous aspects of this interaction are still hardly understood [56]. Proteomic and genomic studies of pathogens and host seem likely to be successful in future to discover the novel strategies for the host and pathogen interactions.

Conclusion:

There are some reasons for inability to eliminate the UTIs in children. Due to the anatomical location of the mea, it is interesting that the urine is normally sterile. A descending infection in the urinary tract can decline when bacteria can descend the urethra. At the same time, chemokines are released while leukocytes are recruited to the site of infection. Adhesion of bacteria to epithelia lining the urinary tract can be prevented by release of constitutive and inducible bactericidal antimicrobial peptides such as α- and β-defensins and cathelicidin, lactoferrin, Tamm-Horsfall protein and lipocalin. Cytokines (IL-1 and TNF alpha) and chemokines (IL-8) activate and attract large numbers of macrophages and neutrophils which damage tubulointerstitial parenchyma with persistence of growing numbers of microorganisms.

Thus, comprehensive information regarding the associated features of the pathogen and host is very necessary for these proposed significant strategies to be completely effective. This review article summarizes some important potential mechanisms in innate immune system for better understanding of its pathophysiology. In spite of the long-term and repeated use of antimicrobial treatment, the common knowledge of the pathogenesis of UTI cannot describe the recurrence of infection, yet.

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