

The role of toll-like receptors (TLRs) in urinary tract infections (UTIs)

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Introduction Urinary Tract Infections (UTIs) are caused by different types of microbial agents such as uropathogenic *Escherichia coli* (UPEC) and *Candida albicans*. The presence of strong physical barriers may prevent the breach of pathogens into the urinary tract. However, sometimes the pathogenic microorganisms may pass through the barriers and stimulate the innate and adaptive responses. Among a variety of innate immune responses, Toll-Like Receptors (TLRs) are one of the most unique and interesting molecules regarding UTIs. Thus, the authors have focused their attention on the role of TLRs in urinary tract defense against pathogenic microbial agents such as UPEC and *C. albicans* through this literature review.

Material and methods Several papers regarding UTIs and TLRs including original and review articles were searched by PubMed and Google Scholar. They were studied and the most important aspects in association with the role of TLRs in UTIs were extracted. Additionally, this paper was prepared using the experience of the authors.

Results The TLRs 2, 4 and 5 are the most functional molecules that contribute to urinary tract defense system and UTIs. It is incredible that TLRs are able to detect and recognize different parts of microbial components relating to the same pathogen. Besides, the flexibility of the TLR molecules may lead to identification of different types of microorganisms with different signaling pathways.

Conclusions Our knowledge associated with TLRs and their activities against microbial causative agents of UTIs may help us to prevent, control and treat UTIs at a higher quality level.

Key Words: UPEC ↔ *C. albicans* ↔ TLR2 ↔ TLR4 ↔ TLR5 ↔ urinary tract

INTRODUCTION

The immune system mechanisms including the innate and the adaptive immunity are activated by the breach of pathogenic microorganisms such as Uropathogenic *Escherichia coli* (UPEC) and *Candida albicans* (*C. albicans*) into the human's urinary tract. So, the junction of physical and immunological mechanisms provide an effective protection for urinary tract against the pathogenic microorganisms. In accordance with several studies, the urothelial cells act as sensitive biosensors which induce the proinflammatory cytokines and other immunologic responses in the presence of pathogens. Moreover, the microbial virulence factors and the quality of the

host's immune responses directly determine the level of urinary tract infections (UTIs) severity from benign to deathful and acute to chronic [1–3].

Among several immune cells, macrophages (MΦs) actively combat with pathogenic microorganisms within diminished epithelial cells. By the entrance of microbial agents into the urinary tract epithelial (urothelial) cells, MΦs produce pro-inflammatory responses and molecules of pathogen recognition receptors (PRRs) at the same time. The PRRs comprise a wide range of molecules such as Nod-like receptors (NLRs) (cytoplasmic proteins), retinoic acid inducible gene (RIG-I)-like receptors (RLRs) (cytoplasmic proteins), C-type lectin receptors (CLRs) (transmembrane proteins), and TLRs (transmembrane

proteins). Among a wide range of innate immune responses against the penetrated pathogenic microorganisms into the host's urinary tract mucosal tissues in parallel with the breach of urothelial cells, TLRs are important parts of innate immune network responses which play a key role in association with the urinary tract defense system and the UTIs prevention. Indeed, TLRs have practically shown their unique potential for a rapid identification of infectious agents and launching signals for elimination of microbial pathogens or activation of adaptive immune responses [4–6].

Thus, the authors have focused their attention on the role of TLRs in urinary tract defense system and UTIs against pathogenic microbial agents such as UPEC and *C.albicans* through this literature review.

Innate immune responses, Inflammation and Pattern recognition receptors (PRRs)

Identification of the innate immune system goes back to 132-63 BC when the Parthian (Iranian) King, Mithridates VI (the King of Pontus) used snake venom to keep his immune system strong against toxins (he is known as the world's first immunologist). From that time until the present, a huge number of immunological mechanisms and cells have been discovered [7].

In recent years, the importance of TLRs has been recognized as a key regulator for innate and adaptive immune responses. The innate immunity is sup-

ported by a variety of natural hindrances including skin and mucosa, nonspecific molecules such as interferons and different types of cells comprising dendritic cells (DCs), MΦs (as the specific immune cells), fibroblasts, endothelial and epithelial cells (as the non-specific immune cells). Immune cells are able to produce and secrete all members of PRR families such as NLRs, RLRs, CLRs, and TLRs. The PRRs like TLRs are important immunologic biosensors for tracing pathogens within the host's cells and tissues by recognition of microbial conserved components, termed pathogen association molecular patterns (PAMPs) [1, 4–6, 8].

Toll-Like Receptors (TLRs)

TLRs are a group of PRR molecules with evolutionary conserved structures that act as the first expressed molecules of the human innate immune system in the presence of the related target ligands. The vital role of toll receptors in association with the innate immune system was first discovered in the insect *Drosophila*. In parallel with progressive discoveries, some homologs of toll receptors were detected in mammals. Today, 10 members of TLRs (TLR1 to TLR10) are recognized in the human innate immune system. These trans-membrane (type I) protein molecules are recognized by the presence of two domains; the first one, an extracellular domain containing leucine rich repeat [LRR (consisting of repeated motifs of 24 amino acids)] which is located in the N-terminal end and binds to its

Table 1. General description of Human's TLRs members, family and their chromosomal location

TLR Family	TLR Member	Chromosomal location	Cellular Localization	Target Ligand	Organism
TLR2	TLR1	4p14	Cell Membrane	Triacyl lipoprotein	Bacteria
	TLR2	4q32	Cell Membrane	Glycoinositolphospholipids, Glycolipids, Lipoarabinomannan, Atypical Lipopolysaccharide (LPS), Lipoproteins, Lipoteichoic Acid, Peptidoglycans, Porins, Zymosan, Heat Shock proteins (HSPs 60, 70, 90)	Bacteria (Gram +ive, Gram –ive, <i>Mycobacterium</i> , Spirochaetes like <i>Treponema maltophilum</i> and <i>Leptospira interrogans</i>), Fungi, Parasites (Protozoa like <i>Trypanosoma cruzi</i>), Self (Host), Viruses
	TLR6	4p14	Cell Membrane	Diacyl lipoprotein	Bacteria (like <i>Mycoplasma</i>), Viruses
	TLR10	4p14	Endolysosome	Triacyl lipoprotein and Diacyl lipoprotein	Bacteria, Viruses
TLR3	TLR3	4q35	Endolysosome	Double Stranded RNA (dsRNA)	Viruses
TLR4	TLR4	9q32-33	Cell Membrane	LPS, Type I and P fimbriae, HSPs 60, 70, 90	Bacteria (Gram –ive bacteria and <i>Chlamydia pneumoniae</i>), Self (Host), Viruses, Fungi (<i>Candida albicans</i>), Protozoa (<i>Trichomonas vaginalis</i>)
TLR5	TLR5	1q33.3	Cell Membrane	Flagellin	Motile bacteria
TLR9	TLR7	Xp22.3	Endolysosome	Single Stranded RNA (ssRNA)	Bacteria, Self (Host), Viruses
	TLR8	Xp22	Endolysosome	ssRNA	Bacteria, Self (Host), Viruses
	TLR9	3p21.3	Endolysosome	Unmethylated CpG-DNA	Bacteria, Fungi, Protozoa, Self (Host), Viruses

proper ligands; and the second one, a conserved and homolog intracellular (cytoplasmic) signaling domain of IL-1 receptor which is known as Toll/IL-1 receptor (TIR) and situated in the C-terminal end. Most of the TLRs adaptors are recognized in the cell membrane and some of them are expressed in sub-cellular endosomal structures. TLRs are produced in a vast range of cells including non-hematopoietic endothelial cells, epithelial cells, parenchymal cells, synovial fibroblasts and hematopoietic originated cells of DCs, MΦs, mast cells, neutrophils, B cells, and T cells. Among 13 identified members of TLRs, 10 members of them comprising TLR1-10 are found in humans. The conserved members of TLR1-TLR9 are found in both humans and mice, while the TLR10 is detected only in humans and the TLR11-13 are identified only in mice [9–12].

According to human TLRs amino acid sequencing investigations, the TLR family members have been divided into five subgroups including TLR2 (TLR1, TLR2, TLR6, and TLR10), TLR3, TLR4, TLR5, and TLR9 (TLR7, TLR8, and TLR9) (Table 1) [2, 6, 10, 12–19].

The expression and distribution of TLRs in human body

The TLR molecules are expressed by a variety of cells in different human tissues. Different types of B and T cells express a diversity of TLRs. MΦs and monocytes actively express the mRNA molecules of TLR1, TLR2, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10. Mast cells which are known as phagocytotic cells express a group of TLR molecules including TLR2, TLR4, and TLR8. The myeloid dendritic cells (MDCs) are able to express and produce TLR1, TLR2, TLR4, TLR5, TLR7, TLR8 and the plasmacytoid dendritic cells (PDCs) are recognized for expressing TLR7, and TLR9. Previous studies show the process of maturation of immature dendritic cells by the presence of PAMPs. So, the expression of TLR1, TLR2, TLR4, and TLR5 in mature dendritic cells in comparison with immature dendritic cells reduces, while the expression of TLR3 only happens in mature dendritic cells. The epithelial cells are important barriers against bacterial infections, because they produce TLR1, TLR2, TLR4, TLR5 and TLR6 in the presence of IFN- γ and TNF- α which leads to proinflammatory reactions [6, 10, 12, 19, 20, 21].

The relationship between TLRs and UTIs

Despite the presence of strong barriers made of urothelial cells in the human urinary tract, sometimes the uropathogenic microorganisms success-

fully enter the urinary tract. By the entrance of uropathogenic microorganisms into the urinary tract, the innate immune responses are going to be activated via expression of the related TLRs within the urothelial cells of bladder (cystitis) and kidneys (nephritis). Consequently, the expression of related TLRs triggers different cascading responses including the release of chemokines, interferons, interleukins, antimicrobial substances and proinflammatory cytokines [1, 6, 12, 14, 17, 19, 20, 22].

With attention to this data, we would like to present the role and the importance of different TLR molecules in UTIs and urinary tract defense system.

TLR1, TLR2, and TLR6

TLR2 usually builds heterodimer structures with TLR1 or TLR6, and each heterodimer complex has its own characteristics and properties. Several studies have shown that, the TLR2 co-receptors including TLR1 and TLR6 have a significant similarity of up to 66% among their amino acid sequences. However, the ligand active sites in TLR1 and TLR6 have a low similarity in their amino acid sequences, which may lead to different conformational structures. These diversities enable TLR2 heterodimers to recognize different PAMPs and ligands. Interestingly, the TLR2 homomers show no considerable functional characteristic in humans. So, in this literature the TLR1-TLR2 and TLR2-TLR-6 heterodimers are studied in separate subtitles. TLR2 proteins are important molecules for recognizing atypical LPS pertaining to non-*Enterobacteriaceae* bacteria (including *Leptospira interrogans*). Among a wide range of target ligands indicated in Table 1, lipoproteins, lipoteichoic acid, peptidoglycans, HSPs (60, 70, 90) and fungal zymosan are important molecules for detecting and identifying UTIs caused by microbial pathogens [6, 9, 10, 12, 19, 23].

TLR1-TLR2

The heterodimer complex of TLR1-TLR2 is able to detect and identify the PAMP molecules of triacylated lipoproteins in *Mycoplasma* spp., *Ureaplasma* sp. and Gram -ive bacteria including *E.coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* which are known as important microbial causative agents of UTIs. Moreover, the other members of *Enterobacteriaceae*, which possess triacylated lipoproteins in their outer membrane, can be recognized by TLR1-TLR2 heterodimers. TLR1 encompasses a hydrophobic channel, which binds to one of the lipid molecules of triacylated lipoproteins. This channel promotes the presence of a triacylated lipoprotein

as a PAMP to be recognized by TLR1. The TLR2 heterodimer binds to the left molecules of triacylated lipoproteins. The crytstallographic studies indicate M-shaped structures in TLR1-TLR2 heterodimers. Lipoproteins are proteins joined with lipids. The lipids are normally bound to NH₂ terminal cysteine in proteins by covalent bonds. Lipoproteins are categorized into two main groups of diacylated and triacylated. Therefore, the complex of TLR1-TLR2 heterodimers plays a key role in association with UTIs caused by Gram -ive bacteria and in particular, the members of *Enterobacteriaceae* like UPEC [3, 9, 11, 12, 19, 23–27].

TLR2-TLR6

In similar to TLR1-TLR2 heterodimers, the extracellular heterodimers of TLR2-TLR6 share a M-form structure. The TLR2-TLR6 heterodimers miss the hydrophobic channel within their structures; therefore these complexes are not able to recognize triacylated lipoproteins. The TLR2-TLR6 heterodimers are able to detect different microbial PAMPs including diacylated lipoproteins in *Mycoplasma* spp., *Ureaplasma* spp., zymosan in fungi particularly in yeasts (such as *Saccharomyces cerevisiae* and *C.albicans*), bacterial lipoteichoic acid in *Staphylococcus* spp., peptidoglycans in Gram +ive bacteria and released microbial HSPs. Besides, the TLR2-TLR6 heterodimers are able to identify the 2 kDa mycoplasmal M Φ activating lipoproteins (MALP). However, the TLR2 proteins are responsible for distinguishing the type of bacterial lipoproteins. The recognition of aforementioned target ligands may lead to release of proinflammatory cytokines. The TLR2-TLR6 heterodimers play a key role for detecting important microbial causative agents of UTIs such as *C.albicans*, *Staphylococcus* spp., *Streptococcus* spp., *Mycoplasma* spp. and *Ureaplasma* spp. It seems that the bacterial triacylated lipoproteins are target ligands for TLR2-TLR10 heterodimers and diacylated lipoproteins are the goal ligands for TLR1-TLR10 heterodimers and TLR10-TLR10 homodimers. However, the role of TLR10 in human innate immune system is unclear [2, 9, 11, 12, 15, 23, 27–34].

TLR3

The infectious viral agents replicate within their infected host cells. The expression of TLR3 as endolysosomal proteins is induced in the presence of dsRNA viruses (Table 1). The TLR3 activates the production of antiviral immune responses by inducing the secretion of pro-inflammatory cytokines and interferon type I. The expression of TLR3 occurs

in the presence of double stranded viruses causing glumeronephritis. However, the role of TLR3 is not major with regard to UTIs [6, 9–12, 14, 20, 33].

TLR4

The most important target ligands for TLR4 molecules are LPS (such as UPEC and other members of *Enterobacteriaceae* family which are related to UTIs), Type I and P fimbriae and HSP molecules of 60, 70, and 90. TLR4 molecules are expressed in the presence of released microbial HSPs pertaining to UPEC, *C.albicans*, etc (Table 1). The majority of UPEC strains encompass the virulence factors of type I fimbriae and FimH (the FimH adhesion is normally located on the top of type I fimbriae). FimH enables UPEC to adhere to uroplakin 1a molecules. The uroplakin 1a molecules are located on the surface of urothelial cells, which line the inner side of the bladder in human urinary tract. So, the attachment of UPEC cells onto the uroplakin 1a molecules induces the TLR4 molecules to eliminate the foreign pathogens from the bladder. Today, we know that TLR4 molecules are expressed in urothelial cells that line the kidneys and the bladder in the urinary tract. The severity of UTIs (UPEC cells number) determines the level of TLR4 molecules expression. For example, the level of secretion of TLR4 molecules in patients with reduced infection of asymptomatic bacteriuria is significantly less than patients with acute and symptomatic UTIs. A healthy immune system is able to clear the urinary tract from microbial pathogens such as UPEC from one up to a few days [1, 3, 4, 9, 11, 12, 14, 19, 20, 35]. The LPS molecules which are situated in the outer membrane of Gram -ive bacteria such as the *Enterobacteriaceae* family members, trigger the expression of TLR4 molecules. The active and effective TLR4 molecules cooperate with MD-2 (a co-receptor molecule which is soluble in the serum and/or attached to the cytoplasmic membrane and/or bound to TLR), LPS binding proteins (LPSBP soluble in serum) and CD14 (soluble in the serum and/or attached to the cytoplasmic membrane and/or bound to TLR). Indeed, the occurrence of this complex makes TLR4 successful to omit the UPEC cells from the urinary tract area. The MD-2 component mediates the attachment of hydrophobic section of LPS onto the extracellular portion of TLR4. Interestingly, the number of fatty chains in lipid A relating to LPS molecule determines the level of TLR4 molecules expression and consequently the level of inflammatory responses. By the invasion of UPEC cells into the urothelial cells of bladder and kidneys, the TLR4 molecules are expressed. Normally, the invaded urothelial

cells dominantly omit the UPEC cells by the help of TLR4 molecules. The presence of type I fimbriae is an evolutionary means for UPEC against immunological responses like TLR4. This virulence factor may dominate the TLR4 defense system and supports the intracellular progression of UPEC cells in urinary tract. So, the bacterial components including LPS, FimH adhesin, type I and P fimbriae in UPEC are recognized as TLR4 inducers in the host's urinary tract. The majority of invasive UPEC cells are resistant to TLR4 molecules and their presence within urinary tract results in chronic and/or complicated cystitis and/or pyelonephritis. Therefore, the malfunction or dysfunction of innate responses, promote the progression of UTIs within the human body [9, 10, 12, 14, 20, 33, 35].

In addition to UPEC cells, the *C.albicans* yeasts trigger the innate immune system via expression of TLR4 proteins. The TLR4 are expressed against *C.albicans* yeasts in different types of candidiasis such as urinary tract candidiasis. In accordance with previous investigations, the expression of TLR4 adaptors is performed via linear and short chains of O-linked mannan polymers. In contrast to TLR2, the expression of TLR4 against *C.albicans* does not lead to secretion of proinflammatory cytokines; it leads to secretion of type I interferons (IFNs). It seems that, the mannose receptors which are contributed to fungal phagocytosis process are blocked for internalizing zymosan throughout the TLR4 adaptors expression. Besides, the recruitment of neutrophils and the secretion of some chemokines decrease significantly [2, 9, 10, 12, 17, 19, 33, 36].

HSP molecules including HSP60, HSP70 and 90 are well known chaperokines which support eukaryotic and prokaryotic cells under normal and stressful situations. The presence of released microbial HSPs may trigger the expression of TLR4 in the host's urinary tract. These chaperokines are recognized in the both cells of UPEC and *C.albicans*. Interestingly, the HSPs are able to link the innate immunity into the adaptive immune mechanisms [10, 13, 30, 37].

TLR5

The expression of TLR5 molecules is induced in the presence of the target ligands of bacterial flagellin protein monomers in the both motile cells of Gram +ive and -ive bacteria (Table 1). Potentially, the flagellin monomers are able to induce proinflammatory cytokines through the expression of TLR5 proteins. UPEC as a typical motile causative agent of UTIs possesses peritichous flagella which induces the expression of TLR5 proteins. So bacterial flagellum, from the evolutionary aspect is known as an effective

virulence factor which contributes to different types of UTIs. The TLR5 molecules are secreted in different types of cells such as urothelial cells of bladder (highly expressed) and kidneys (low expression). As the TLR5 adaptors are normally secreted in the basolateral parts of the cells, the intracellular presence of UPEC strains within the urothelial cells leads to expression of TLR5 proteins as a key signal for the UTIs. The innate immune proteins of TLR5 are important molecules in urinary tract defense system and UTIs. Several studies indicate that the UPEC cells cheat the local innate immune system in bladder; because the UPEC cells switch off the expression of their flagella genes in bladder and switch on theirs in the host's kidneys. This bacterial characteristic explains how the UPEC cells evade the innate immune mechanisms via their adaptation to their environmental situations [10, 20, 26, 35, 38, 39].

TLR7, TLR8, and TLR9

As can be seen in Table 1, bacterial and viral ssRNAs are target ligands for TLR7 and TLR8 proteins and microbial unmethylated CpG-DNAs are the appropriate target ligands for TLR9. So, the expression of TLR7 and TLR8 molecules is triggered in the presence of bacterial and/or viral ssRNAs while the TLR9 molecules are expressed in the presence of unmethylated CpG DNA motifs belonging to bacteria, fungi, viruses and protozoa. These members are able to discriminate the nucleic structures within their own structures. However, TLRs 7 and 8 are not expressed during UTIs. In contrast to TLRs 7 and 8, TLR9 has a key role against cytomegaloviruses. A cytomegalovirus infection can be deadly for patients with kidney infections after kidney graft operations [10, 19, 20, 33, 40].

CONCLUSIONS

It has been revealed that TLRs are incredible molecules with sharp sensitivity and specificity for detecting and identifying a wide range of microbial components. Among a vast range of innate immune responses, they act rapidly and are able to be expressed in different parts of the human body. It is unbelievable that multifunctional molecules of TLRs are able to be expressed by different types of pathogens in different types of infectious diseases. These fabulous biosensors do their best try to protect the host's body against microbial infections. However, sometimes they have to be supported by the adaptive immune system. When TLRs are not able to overcome the pathogens, they switch from the innate immune system into the adaptive immune

system. Regarding UTIs, there are different types of TLRs which can protect the host's urinary tract from pathogenic microorganisms including bacteria, fungi and viruses with a diversity of mediators, complexes and signaling pathways. Finally, TLR2, TLR4 and TLR5 are the most competent molecules in urinary tract defense system. These molecules are the most effective TLRs against UTIs. This in-

valuable knowledge may help us to prevent, control and treat UTIs at a higher quality level. Simultaneously, in order to have a definite treatment, there is a vital need for advanced molecular diagnostic tools such as microarray.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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