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International Journal of Antimicrobial Agents 31S (2008) S9–S14

INTERNATIONAL JOURNAL OF Antimicrobial Agents

www.ischemo.org

Impact of Toll-like receptor signalling on urinary tract infection

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Abstract

Toll-like receptors (TLRs), components of the innate immune system, play a pivotal role in the pathogenesis of urinary tract infection (UTI). TLRs (especially TLR4) expressed both by epithelial and non-epithelial cells, e.g. monocytes, initiate appropriate immune and inflammatory responses to defend and overcome microbial invasion and infection. Virulent uropathogenic strains (*Escherichia coli*) express P fimbriae, which bind to glycolipid receptors of uroepithelial and kidney tubular cells, triggering TLR4 activation with subsequent recruitment of leukocytes and release of pro-inflammatory cytokines. Tamm–Horsfall glycoprotein (uromucoid), a kidney-specific glycoprotein, not only binds to fimbriated *E. coli* and activates complement and dendritic cells, but also apparently shows an immunoregulatory function in UTI via a TLR4-dependent mechanism. Dysregulation of TLR and chemokine candidate genes (e.g. *CXCR1*) might predispose patients to chronic recurrent UTI. TLR antagonists and agonists can influence host defence mechanisms, and some of these immunomodulating agents may help to overcome intrinsic disturbances of the TLR system to offer new therapeutic options in UTI.

Keywords: Toll-like receptor; TLR4; Urinary tract infection; Uropathogens; Virulence factors; *Escherichia coli*; Defence mechanisms; Kidney cells

1. Introduction

Urinary tract infections (UTIs) and related complications, such as chronic recurrent UTI, chronic bacterial interstitial nephritis and urosepsis, still constitute a severe problem in the clinical setting, placing a high burden on medical resources and public health budgets [1]. A patient's individual susceptibility to develop UTI varies greatly, and for a long time the pathophysiological background and molecular basis of specific host defence mechanisms remained unknown. During recent years, a panel of virulence factors of pyelonephritic bacteria became apparent, e.g. adherence factors, cytotoxins, the potency to downregulate mucosa-protective secretory immunoglobulin A (IgA) (polymeric immunoglobulin receptor) in kidney cells and deficiency of IgG subclasses [1,2]. Persistence of bacterial antigen in the renal tissue (mainly interstitium) might be an additional factor in the pathogenesis of chronic bacterial nephritis [3–6], clinically defined by low-count bacteriuria, tubular proteinuria, impaired concentration ability, elevated cystatin C serum levels and typical signs as assessed by ultrasound and intravenous urography [3–7]. Recently, the detection of Toll-like receptors (TLRs) allowed a deeper insight into the potential role of innate immunity in protecting the mucosal barrier against attack by bacteria, especially by uropathogenic *Escherichia coli*, which account for >80% of acute non-obstructive pyelonephritis and acute uncomplicated cystitis [8–10].

2. TLRs: mediators in host immune recognition

TLRs are specific components of the innate immune system. They belong to the group of so-called pattern recognition receptors (PRRs). TLRs are located on leukocytes (TLR1, TLR2), especially peripheral blood monocytes (TLR2, TLR4), macrophages, immature dendritic cells, natural killer cells, and T- and B-cells (TLR7, TLR9, TLR10) as well as on tissue cells (enterocytes, kidney epithelial cells, mesangial cells). TLRs sense and recognise distinct pathogen-associated molecular patterns by homophilic and heterophilic interaction in order to defend mucosal barriers through activating immune cells and pro-inflammatory

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doi:10.1016/j.ijantimicag.2007.07.032

cytokines. The TLR system, evolutionary conserved across various species of microorganisms, consists of 12 presently known members; up to 11 TLRs were identified in humans. TLRs interact with various endogenous and exogenous ligands. After binding, e.g. to lipopolysaccharide (LPS) (TLR4), peptidoglycans (TLR2), viral (double-stranded) RNA or DNA motifs (TLR3), extracellular matrix components, heat shock proteins, synthetic lipopeptides and oligodeoxynucleotides, TLR signals produce an inflammatory response via the nuclear transcription factor NF-κB, which activates cells to secrete cytokines such as interleukin-1β (IL1-β), IL-6 and tumour necrosis factor-alpha (TNFα) (Fig. 1). As patient-related immunomodulating factors, TLRs are closely involved in pathogen recognition and host defence in UTI [8,9].

Efficient host defence towards bacterial virulence factors in UTI depends on the engagement and response of both the adaptive and innate immune systems (e.g. complement factors, TLR). TLR4 (the human TLR4 gene mapped to chromosome 9q32q33) was the first PRR to be identified exhibiting a specific ligand: as an example, bacterial endotoxin (LPS) is recognised by a receptor complex of CD14, LPS-binding protein (LBP), TLR4, and the accessory MD-2 component. LPS is transferred to membrane-bound CD14 (mCD14) by LBP, where CD14 presents LPS to the TLR4–MD-2 receptor protein complex. MD-2, an anchorless protein, is a homologue of MD-1, which is a B-lymphocyte secretory protein. MD-2 allows TLR4 to work, since MD-2 gene knockout mice do not respond to LPS. However, under certain circumstances, TLR4 signalling can be activated in the absence of CD14 and MD-2 (see below) [11].

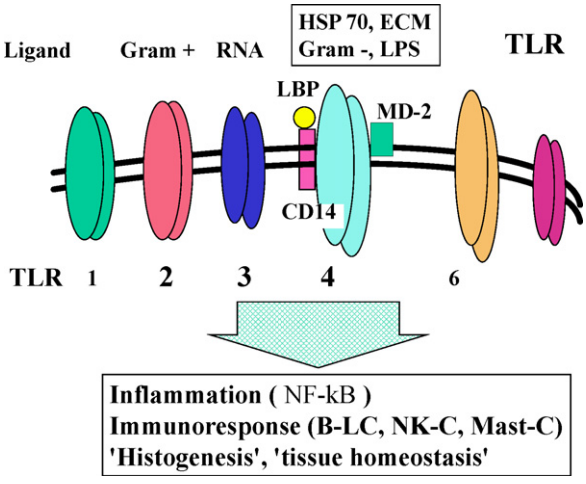

Fig. 1. Schematic presentation of membrane-surface-bound Toll-like receptors (TLRs) (host cells, monocytes, kidney target cells) and selected ligands. A subpopulation of TLRs is localised in intracellular endosomal compartments. Individual TLRs recognise different microbial constituents and follow different signalling pathways using distinct adaptor molecules. HSP, heat shock protein; ECM, extracellular matrix component; LPS, lipopolysaccharide; CD14, endotoxin receptor; MD-2, accessory component; LBP, LPS-binding protein; NF-κB, nuclear transcription factor; B-LC, B-lymphocytes; NK-C, natural killer cells; Mast-C, mast cells.

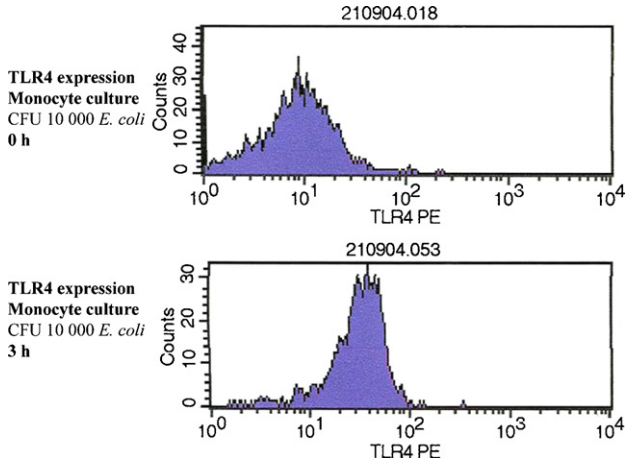

Fig. 2. Upregulation of Toll-like receptor 4 (TLR4) by cultured human monocytes following incubation with whole Gram-negative bacteria. Scatter diagram revealing TLR4 fluorescence intensity of CD14-positive monocytes before (0 h) and 3 h after incubation with 10 000 colony-forming units of *Escherichia coli*. Antigen shift to the right indicates activation of monocyte TLR4 compared with the isotype controls. (For methods, see [14–17].)

Other ligands of TLR4 are of non-microbial origin (see Fig. 1). On the other hand, Gram-positive bacteria (proteoglycan, lipoteichoic acid), glycolipids, zymosan (fungi) and atypical LPS interact with TLR2 [12,13]. Activation of TLR4 recruits myeloid differentiation primary response protein 88 (MyD88), an intracytoplasmic downstream adaptor molecule, which activates inflammation, proliferation and apoptosis. Cultured human peripheral blood monocytes that were incubated with whole bacteria (*E. coli*) rapidly upregulated the expression of membrane-surface-bound TLR4, thus demonstrating TLR4 as a central constituent of the human endotoxin (LPS) sensor molecule [14] (Fig. 2). In addition, bacterial flagellin, the component of bacterial flagella and secreted by commensal and pathogenic bacteria, contacts basolateral epithelial surfaces and induces pro-inflammatory genes via interaction with TLR5 [18].

3. Type 1 fimbriae/P fimbriae and TLR4 activation

Since nephropathogenic bacteria, e.g. *E. coli*, may cause live-threatening complications (urosepsis), TLRs as host constituents of innate immunity recognising a broad panel of microbial products are the focus of basic and clinical research [19]. TLRs detect, control and discriminate the pathogenic potential of microbes and trigger the mucosal host defence, resulting in clearance of bacteria or, in the cases of dysbalance of the innate immune response, leading to septic complications and even death: this addresses complicated forms of UTI in at-risk patients such as those undergoing immunosuppressive therapy (organ transplantation, cancer patients undergoing chemotherapy), patients suffering from long-lasting diabetes mellitus, multiple myeloma and primary immunodeficiency syndromes [7,20,21] (Fig. 3).