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Toll-Like Receptor 11: Role in Post-Transplantation Renal Infections

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Abstract

Uropathogenic microorganisms interact with the intestinal tract mucosa, which activate immune cell responses through the Toll-like receptors (TLRs).TLRsare single, membrane-spanning, non-catalytic proteins and they play significant role in the innate immune system. Recent studies have demonstrated that TLRs expressed in sentinel cells such as dendritic and macrophages cells that recognize structurally conserved molecules derived from microorganisms. Interestingly, the massive infection of the kidney observed in the TLR11 knockout mice, which indicate the hypothesis that TLR11 provides a barrier that prevents uropathogenic bacteria from infecting specifically the post-transplantation kidneys and therefore provide a new perspective on the host-pathogen interactions.

Keywords: Toll-like receptors; TLR11; Uropathogenic bacteria; Post-transplantation Infection; Toxoplasma gondii

Introduction

There are several types of the toll-like receptors (TLRs) that have been identified till date, namely; TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, TLR11, TLR12, and TLR13 [1]. TLRs protein sequences have maximum homology with the protein coded by the toll gene, which is identified in Drosophila [2]. TLRs comprise a family of type I transmembrane proteins, each with anextracellular N-terminal domain consisting of multiple leucine-rich repeat (LRR) region involved in ligand binding, as well as a C-terminal cytosolic region containing a Toll/interleukin-1 receptor (TIR) domain that mediates recruitment of signaling components [3]. Based on existing structures of TLR ectodomains, the activated, ligand-bound state appears to be a dimer [4-7]. Most of the TLRs use common signaling adaptor molecules, MyD88 (myeloid differentiation primary response gene 88) and/or TRIF (TIR domain-containing adaptor inducing interferon-b), to initiate signaling [3].

TLR and immunity

In humans, both innate and adaptive immune responses have developed as defense system against contagiousmicrobes. TLRs have asignificantrole in the detection of invading microbes. They have been identified as the first receptors, which detect infectious microorganisms and induce the immune response. Furthermore, TLRs play a vital role in associating the innate and adaptive immune responses [8]. TLRs play crucial roles in the innate immune system by recognizing pathogen-associated molecular patterns (PAMPS) derived from numerous microbes. TLRs signal through the recruitment of specific adaptor molecules, leading to activation of the transcription factors nuclear factor of kappa-light-chain-enhancer of activated B cells (NF-κB) and interferon regulatory factors (IRFs), which dictate the result of innate immune responses. TLR signaling appears to be divergent and plays an important rolein many aspects of the innate immune responses to given pathogens [9].

Murine infection with the intracellular protozoan parasite Toxoplasma gondiiprovides an excellent model for studying the effects of, the absence of normal TLR recognition, on infection induced hostresponses. Since a major TLR-TLR ligand interaction has been identified by Yarovinskyet.al.,(2005) [10] that governs innate immunity to this pathogen. In another study, Yarovinskyet. al., (2008) [11] further systematically examined cellular responses of TLR11 knockoutmice at early time points after i.p. parasite inoculation. Unexpectedly, they found that in the absence of TLR11, mice developed a marked immunopathological response associated with Natural Killer (NK) cell IFN- γsecretion.

Significance of TLR11

Many investigators have tried to study, the significance of TLR11 against uropathogens lately. Recent study using transfection of TLR11 together with a reporter gene into various cell lines yield weak responses to PAMP [12] and in CHO cells or HEK-293 cells expressing TLR11, Toxoplasma gondii profilin protein (TPRF) stimulation resulted in modest activation of an NF-κB reporter [10]. Another study of TLR11 recognition of FliC also produced only weak activation of an NF-κB reporter gene [13,14]. Consequently it was found that innate recognition of TPRF through TLR11 requires the presence of TLR12 [15]. However, even with co-expression of both TLR11 and TLR12, the response of NF-κB reporter genes to TPRF is relatively poor [16]. Whether or not there are additional co-factors required for recognition of FliC by TLR11 remains unclear. Subsequently, it will be necessary to explore the role of specific TLR11 domains in the TPRF and FliC response through genetic engineering of murine innate immune cells. Additional studies will be needed in order to distinguish between the requirements for binding and the domains of TLR11, which are required for signaling with or independent of TLR12 [12].

Post-transplantation infections

Among the most common post-transplantation infectious diseases, urinary tract infections (UTIs), including asymptomatic bacteriuria, cystitis and pyelonephritis, are a major cause of human morbidity and mortality [17-18].UTIs are also the most common form of bacterial

infection in renal transplant recipients [19-20]. It is generally agreed that post-transplantUTIs are caused by exposure to pathogens as a result of surgical procedures (i.e. urethral and ureteral stent catheters) and long-term immunosuppressive therapy [20-21]. Uropathogenic Escherichia coli (UPEC) strains are the major cause of UTIs. They are enclosed with a range of virulence factors including flagella, transporter proteins, fimbrial adhesins, invasins, iron-acquisition systems and toxins that are jointly facilitating the bacteria to attack host tissues and effectively establish the infection [22-27].The massive infection of the kidney observed in the TLR11 knockout mice supports the hypothesis that TLR11 provides a barrier that prevents uropathogenic bacteria from infecting the kidneys [13].

The studies on TLR11 assume significance in the wake of its association with binding of specific ligand present on Salmonella typhii as demonstated by Mathuret. al.,2012[14]. They have further shown that TLR11 knockout mice were significantly infected with S. typhii. Moreover, S.typhii is a human pathogen that causes typhoid fever. As data indicated that due to typhoid fever, more than 20 million people are affected globally, in which 220 thousands deaths occur per year. Therefore, it is necessary to carry out further studies on mechanism of action of TLR11 and association with salmonella and other human pathogens.

Similarly, Shi et. al., 2012 [28] found that highly invasive Salmonella induced Peyer patch bleeding in the TLR11 knock-out mouse, a phenotype resembling human Salmonella infection. Results also stated that TLR4 and TLR11 may work as “blocker-TLRs” of Salmonella to prevent highly invasive Salmonella from penetration into the murine Peyer patches and spreading systemically. TLR11 plays an important role in preventing murine intestinal infection and therefore might provide a new perspective on the host-microbes interactions.

However, Song et. al., 2016 [29] reported that the infection studies conducted in 4 different laboratories have found that TLR11-deficient mice do not show enhanced susceptibility to S. Typhi regardless the route of inoculation. They observed no binding of flagellin to TLR11and found no differences in the response of wild-type and TLR11-deficient mice to the administration of bacterial flagellin.

Further studies are therefore required to establish the exact mechanism of binding of TLR11 with Salmonella typhii.

Expression of TLR11

TLR11 is abundantly expressed in the mice bladder, where it probably shares the burden of responding to UPEC with TLR4, but in the kidney, TLR11 alone appears to be responsible for mounting innate immune responses [13]. Based on the sequence of the human genome in the NCBI-GenBank and the genomic sequence of some human cell lines, it appears that humans might not express full-length TLR11 protein due to the presence of a stop codon within its coding region [30].Through the use of CRISPR-Cas9 technology [31], stop codon in human TLR11 can be removed andIt is alsopossible that the stop codons in the ORF of human TLR11 might represent a form of genetic polymorphism, similar to the situationobserved for TLR5 in which a stop codon within the ORF of human TLR5 in many individuals makes them incapable of responding adequately to flagellated bacterium [32].The presence or absence of TLR11 from the human population or only from a subpopulation can be done by systematic analysis of TLR11 sequences. However, it is tempting to speculate that one of the reasons humans are particularly susceptible to UTIs is because the absence of TLR11 has removed a defense pathway with the unique ability to specifically recognize UPEC(Figure 1)[13].

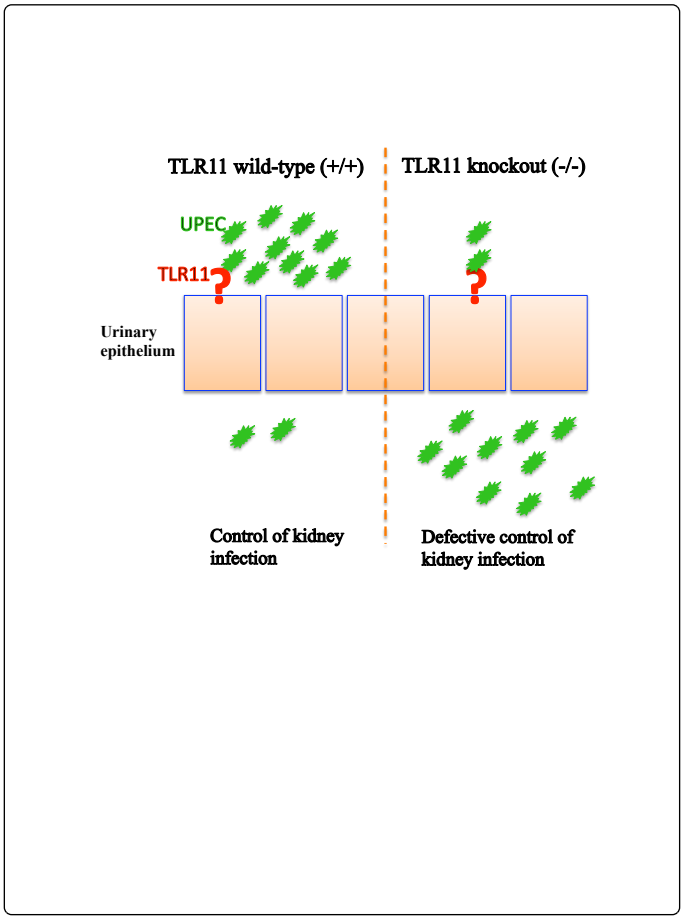

Figure 1.Schematic representation ofinfection of kidneys of TLR11 knockout mice by UPEC. Significantly greater numbers of bacterial cells were observed in the kidneys of knockout TLR11 mice compared with wild-type mice, even though equal numbers of bacteria were used to infect the animals. This model projected from the Zhang et.al., 2004 [13]. UPEC, Uropathogenic Escherichia coli.

Yarovinsky et. al., 2008 [11] demonstrated that in the absence of TLR11, a major TLR involved in recognition of Toxoplasma gondii, infection with this protozoan parasite induced an abnormal immunopathological response consisting of pancreatic tissue destruction, fat necrosis, and systemic elevations in inflammatory reactants.

Further, Yarovinsky et. al., 2008[11] in their study with T. gondii model, absence of TLR11 pattern-recognition of the parasite led to profound immunopathology affecting pancreatic and other host tissues during an acute infection time frame in which TLR11 deficiency did not result in significantly increased pathogen load. This finding though at first glance appears, paradoxical since T. gondii-infected TLR11/ mice were previously shown to display markedly reduced systemic IL-12 production in earlier study [10]. Nevertheless, a residual IL-12 response was observed in the TLR11/animals and, consistent with this observation, the knockout mice developed significantly increased IFN- levels. Recently, Gonzalez et. al., 2014 [33] demonstrated that Profilin-

like protein in Toxoplasma gondii used as a TLR11 ligand and Hataiet. al., 2016 [12] shown that it also recognizes flagellin (FliC) from E. coli and Salmonella typhimurium.

Melo et. al., 2010 [34] observed using UNC93B1-deficient mice, in which the coactivation of TLRs 3, 7 and 9 by RNA/DNA is abolished. More recently, a series of studies have shown that the TLR11-mediated response to T. gondii is compounded by coactivation of TLR12, as well as TLR7/TLR9 triggered byparasite RNA/DNA [35]. In the absence of all these pathways combined, mice show susceptibility phenotype that resembles T. gondii infected MyD88-deficient hosts [33]. Taking all these observations together with the fact that humans have a truncated nonfunctional TLR11 gene and no homolog for mouse tlr12, they have proposed that TLR5 'fills in' for the absent human TLR11 [33].

Conclusion

In the wake of important role of TLR11 in uropathogenic infections, as mentioned in the studies cited above, we propose that through the use of CRISPR-Cas9 technology, stop codon in human TLR11 can be removed. TLR11 could be target for drug design to prevent the post-transplantation kidney infections as well as other such infections affecting large human populations. Moreover, elucidation of role of TLR 11 in kidney should eventually allow us to manipulate them in strategies to treat various post-transplantation renal infections, which are reaching dangerous proportions due to increasing diabetic-associated renal failure globally.

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