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

Indra Mani* and Kavita Vasdev

Department of Microbiology, Gargi College, University of Delhi, Siri Fort Road, New Delhi, India

*Corresponding author: Indra Mani, Department of Microbiology, Gargi College, University of Delhi, Siri Fort Road, New Delhi, India, Tel: 91-9811873144; E-mail: atvikav@gmail.com

Rec date: May 30, 2017; Acc date: July 01, 2016; Pub date: July 03, 2016

Abstract

Uropathogenic microorganisms interact with the intestinal tract mucosa, which activate immune cell responses through the Toll-like receptors (TLRs). TLRs are 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 indicates 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 an extracellular 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. The presence of a cytosolic region containing one or more TIR domains 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 contagious microorganisms. TLRs have asignificant role 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 microorganisms. 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-kB) and interferon regulatory factors (IRFs), which dictate the result of innate immune responses. TLR signaling appears to be divergent and plays an important role in many aspects of the innate immune responses to given pathogens [9].

Murine infection with the intracellular protozoan parasite Toxoplasma gondii provides an excellent model for studying the effects of, the absence of normal TLR recognition, on infection induced host responses. Since a major TLR-TLR ligand interaction has been identified by Yarovinskaya et al. (2005) [10] that governs innate immunity to this pathogen. In another study, Yarovinskaya et al. (2008) [11] further systematically examined cellular responses of TLR11 knockout mice 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-γ secretion.

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-kB reporter [10]. Another study of TLR11 recognition of Flic also produced only weak activation of an NF-kB 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-kB 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 infections.
infection in renal transplant recipients [19-20]. It is generally agreed that post-transplant UTIs 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 demonstrated 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. Typhii regardless the route of inoculation. They observed no binding of flagellin to TLR11 and 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 and it is also possible that the stop codons in the ORF of human TLR11 might represent a form of genetic polymorphism, similar to the situation observed 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].

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-

Figure 1. Schematic representation of infection 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.
like protein in Toxoplasma gondii used as a TLR11 ligand and Hantaet 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 by parasite 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.

Acknowledgments

Authors gratefully acknowledge Principal, Gargi College for providing the infra-structure and reviewers for their invaluable suggestions and comments which helped in improving the manuscript.

References

1. Mahla RS (2013) Sweeten PAMPs: Role of ‘sugar’ coated PAMPS in innate immunity and vaccine biology. Front Immunol 2: 240.
2. Hamson GK, Edfeldt K (2005) Toll to be paid at the gateway to the vessel wall. Arterioscler. Thromb Vasc Biol 25: 1085-1087.
3. Kawai T, Akira S (2010) Toll-like receptors. Nat Immunol 11:373-384.
4. Choe J (2005) Crystal structure of human Toll-Like receptor 3 (TLR3) ectodomain. Science 309:581-585.
5. Liu L, Botos L, Wang Y, Leonard JN, Shinouchi J, et al. (2008) Structural basis of toll-like receptor 3 signaling with double-stranded RNA. Science 320: 179-181.
6. Park BS, Song DH, Kim HM, Choi BS, Lee H, et al. (2009) The structural basis of lipopolysaccharide recognition by the TLR4–MD-2 complex. Nature 458: 1191-1195.
7. Liu J, Sun PD (2012) The structure of the TLR5-flagellin complex: a new mode of pathogen detection, conserved receptor dimerization for signaling. Sci Signal 5: 11.
8. Trejo-de la Oa, Hernández-Sánchez P, Maldonado-Bernal C (2014) Relevance of single-nucleotide polymorphisms in human TLR genes to infectious and inflammatory diseases and cancer. Genes Immuin 15: 199-209.
9. Kawasaki T, Kawai T (2014) Toll-like receptor signaling pathways. Frontiers in immunology 5: 1-8.
10. Yarovinsky F, Zhang D, Andersen JF, Hammberg GL, Serhan CN, et al. (2005) TLR11 activation of dendritic cells by a protozoan profilin-like protein. Science 308: 1626–1629.
11. Yarovinsky F, Henry S, Sher A (2008) Recognition of Toxoplasma gondii by TLR11 Prevents Parasite-Induced Immunopathology. J Immunol 181:8478-8484.
12. Hati H, Lepelley A, Zeng W, Hayden MS, Ghosh S (2016) Toll-Like Receiver 11(TLR11). Interacts with Flagellin and Profilin through Disparate Mechanisms. PLoS ONE 11(2): e0149897.
13. Zhang A, Zhang G, Hayden MS, Greenblatt MB, Busey C, et al. (2004) Toll-like Receptor That Prevents Infection byUropathogenic Bacteria. Science305:1522-1526.
14. Mathur R, Obi H, Zhang D, Park SG, Soo J, et al. (2012) A mouse model of Salmonella typhi infection. Cell 151: 596-596a.
15. Kobalansky AA, Janikovic D, Oh H, Henry S, Sungnak W, et al. (2013) Recognition of profilin by toll-like receptor 12 is critical for host resistance to Toxoplasma gondii. Immunity 38: 119-130.
16. Raett M, Khairdin A, Sturge CR, Pider R, Li H, et al. (2013) Cooperation of TLR12 and TLR11 in the IFR8-dependent IL-12 response to Toxoplasma gondii profilin. J Immunol 191: 4818-4827.
17. Foasam B, Brons P (2003) Epidemiology of urinary tract infections, transmission and risk factors, incidence, and costs. Infect Dis Clin North Am 17:227-241.
18. Johnson JR, Russo TA (2005) Molecular epidemiology of extraintestinal pathogenic (ureapathogenic) Escherichia coli. Int J Med Microbiol 295:385-403.
19. Takai K, Aoki A, Suga A, ToIkemura J, Wilczek HE, et al. (1998) Urinary tract infections following renal transplantation. Transplant Proc 30:3140.
20. Schmidtmnt S, Dittrich E, Hott WH (2002) Urinary tract infections after renal transplantation. CurrOpinUrol 12:125-130.
21. Goya N, Tanabe K, Iuchi Y, Oshtina T, Yagiawa T, et al. (1997) Prevalence of urinary tract infection during outpatient follow-up after renal transplantation. Infectation 25:101-105.
22. Lin Y, Bogdan M, Tong S, Gau Z, Zheng L (2016) Substrate selectivity of lysophospholipid transporter LptP involved in membrane phospholipid remodeling in Escherichia coli. J Biol Chem 29: 2136-2149.
23. Fuerst O, Lin Y, Granell M, Leblanc B, Padrés E, et al. (2015) The melibiose transporter of Escherichia coli:critical contribution of hps-377 to the structural organization of the interacting substrate binding sites. J Biol Chem 290:11-11.
24. Dodoen KW, Jacob-Dubuisson F, Striker RT, Hultgren SJ (1993) Outer-membrane PapC protein. Science 308: 1626–1629.
25. Waliabur A, Puthia M, Wiser A, Gir C, Dier S (2016) Uropathogenic Escherichia coli strain CFT073 disrupts NLRP3 inflammasome activation. J Clin Invest 126: 2425-2436.
26. Shi Z, Cai Z, Ye J, Zhang T, Zhao S, et al. (2012) Toll-like Receptor 11 (TLR11) Prevents Infection byUropathogenic Bacteria. Science303:1522-1526.
27. Zhou G (2001) Uropilakina is the urethral receptor for uropathogenic Escherichia coli: evidence from in vitro FimH binding. J Cell Sci 114: 4095-4103.
28. Uttel GC, Totsika M, Schade K, Carey AL, Sweet MJ, et al. (2013) UropathogenicEscherichia coli virulence and innate immune responses dur-ing urinary tract infection. Curr Opin Microbiol 16: 100-107.
29. Waldburger A, Puthia M, Wiser A, Gir C, Dier S (2016) Uropathogenic Escherichia coli strain CFT073 disrupts NLRP3 inflammasome activation. J Clin Invest 126: 2425-2436.
30. Shi Z, Cai Z, Ye J, Zhang T, Zhao S, et al. (2012) Toll-like Receptor 11 (TLR11) Prevents Infection byUropathogenic Bacteria. Science303:1522-1526.
31. Songl, WilhelmCL, Wengl T, Maira-Litran T, Seung-Joo L (2016) Absence of TLR11 in mice does not confer susceptibility to Salmonella Typhi. Cell 164: 827-828.
32. Ishii KJ, Uematsu S, Akira S (2006) Toll-1 gates for future immunotherapy. Curr Pharm Des 12: 4135-4142.
33. Caperci, MR (2005) Gene targeting in mice: functional analysis of the mamalian genome for the twenty-first century. Nat Rev Genet 6:507-512.
34. Hawn TR, Verbon A, Lettinga KD, Zhao LP, Li SS, et al. (2003) A common dominant TLR5 stop codon polymorphism abolishes flagellin signaling and is associated with susceptibility to legionnaires’ disease. J Exp Med 198:153-152.
35. Gonzales RMS, Michael J, O’connell HS, Yang Y, Moreno-Fernandez ME, et al. (2014) Toxoplasma gondii-Derived Profilin Triggers Human Toll-Like Receptor 5-Dependent Cytokine Production. J Innate Immun 6:685-694.
36. Melo MB, Kasperkowicz P, Cerny A, Konen-Waisman S, Kurt-Jones EA, et al. (2010) UNC93B mediates host resistance to infection with Toxoplasma gondii. PLoS Pathog 6: e1001071.
37. Andrade WA, Souza Mdo C, Ramos-Martinez E, Nagpal K, Dutra MS, et al. (2013) Combined action of nuclear acid-sensing toll-like receptors and TLR11: TLR12 heterodimers imparts resistance to Toxoplasma gondii in mice. Cell Host Microbe 13:42-53.