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Interrelationship between Toll-like receptors and infection after orthotopic liver transplantation

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Abstract

Early microbial recognition by the innate immune system is accomplished by Toll-like receptors (TLRs), with resultant initiation of a pro-inflammatory response against infecting organisms. In spite of presence of an abundance of Toll-like receptors on the surface of the liver, gut bacteria does not elicit an inflammatory reaction in healthy individuals due to tolerance to these TLRs, suggesting that the inflammatory responses seen in the liver are the result of breakdown of this tolerance. While orthotopic liver transplantation is often life saving in many instances, death following this procedure is most commonly due to infection that occurs in up to 80% of transplant recipients, most commonly due to microbial causes in up to 70% of cases and viral infections in 20%, while fungal infections affect only 8% of cases. The probability of acquiring infection following hepatic transplantation is heightened due to affection of the innate immune defense mechanisms of the host following this procedure. Single nucleotide polymorphisms of TLRs have been associated with increased likelihood of either development of post-transplant infection or eradication of infecting organism. However, conflicting reports from other studies reveal that prevalence of this single nucleotide polymorphism is not increased in infected patients.

Key words: Toll like receptors; Infection; Liver transplantation; Cirrhosis; Immunity; Orthotopic

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Core tip: Microbial recognition by the innate immunity is accomplished by Toll-like

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receptors (TLRs). In spite of presence of an abundance of TLRs on the surface of the liver, gut bacteria does not elicit an inflammatory reaction in healthy individuals due to tolerance to these TLRs suggesting that the inflammatory responses seen in the liver are the result of breakdown of this tolerance. The probability of acquiring infection following hepatic transplantation is heightened due to affection of the innate immunity of the host. There is controversy about the association between genetic polymorphism of TLRs with the development of post-transplant infection.

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INTRODUCTION

Host protection against invading pathogens is dependent on the coordinated reactions of both innate and adaptive immune systems beginning with the early detection and subsequent initiation of a pro-inflammatory response against infecting organisms^[1], while the adaptive immune system is responsible for pathogen removal in the later stages of infection and creation of immunological memory^[2]. Early microbial recognition by the innate immune system is done by use of germ-line encoded pattern recognition receptors (PRRs) capable of identifying molecular arrangements particular to the invading microbe known as pathogen-associated molecular patterns (PAMPs) as well as those arising from direct injury to host cells termed damage-associated molecule patterns (DAMPs)^[3,4].

Recognition of PAMPs and DAMPs is carried out by a subgroup of PRRs called Toll-like receptors (TLRs) of which there are ten identified human types. These receptors consist of a membrane-spanning glycoprotein and a 200 amino acid region in their highly conserved C-terminal known as the Toll/IL-1R (TIR) domain^[4]. While TLR4 was the first TLR to be identified mainly for its recognition of lipopolysaccharide (LPS) such as that present in the outer membranes of Gram-negative bacteria, every TLR subsequently identified has the ability to recognize specific sequences of PAMPs. Furthermore, on the basis of subcellular localization, TLRs can be classified into two main groups. TLRs 1, 2, 4, 5, and 6 are receptors situated on the cell surface and are primarily responsible for recognition of bacterial PAMPs, while TLRs 3, 7, 8, 8, and 11 are intracellular receptors for detection of viral PAMPs and DNA. TLR 11 also has the added ability to recognize uropathogenic bacteria^[5].

Joining of the Toll-receptor with its respective ligand, by way of its leucine-rich repeat (LRR) domain, initiates a downstream cascade resulting in upregulation of pro-inflammatory cytokines and chemokines and signaling of interferon secretion. While TLRs are primarily a part of host innate immunity, they connect the innate with the adaptive immune systems by playing a role in dendritic cell maturation, antigen presentation, and T and B-cell recruitment and activation^[6], immune reactions that are important in host infection with viral agents, including hepatitis C virus (HCV) infection. Initiation of the afore mentioned signaling cascade occurs by joining of the TIR domain to any of four primary adaptor molecules, namely myeloid differentiation factor 88 (MyD88), TIR-domain containing adaptor-inducing interferon-beta (TRIF), TIR-associated protein (TIRAP), and TRIF-related adaptor molecule (TRAM)^[7].

All TLRs utilize MyD88 except TLR3 that employs TRIF. TLRs 2 and 4 signaling requires TIRAP in conjunction with MyD88, while induction of antiviral interferon response and stimulation of nuclear factor kappa B (NFκB) by TLR 3 and 4 is dependent on TRIF, the TLR4-TRIF signaling pathway further utilizing TRAM^[6]. Both MyD88-dependent and -independent pathways are vital signal transduction pathways that enable host TLRs to initiate immune reactions in response to recognition of pathogenic microorganisms including hepatitis viruses B and C^[8,9].

TLRS AND LIVER

The liver is the first defensive structure against bacteria and their derivatives persistently received from the gut by way of the portal circulation^[10]. In spite of

presence of an abundance of TLRs on the surface of parenchymal, as well as non-parenchymal, hepatic cells^[8], the continuous exposure of hepatic cells to gut bacteria does not elicit an inflammatory reaction in healthy individuals, demonstrating the development of a type of tolerance to TLR ligands and giving rise to the suggestion that the inflammatory responses seen in the liver are the result of breakdown of this tolerance^[11].

Kupffer cells

Stimulation of TLRs 2, 3, 4, and 9 expressed on hepatic Kupffer cells faced with gut pathogen associated molecular patterns (PAMPs) leads to generation of a number of cytokines including tumour necrosis factor α (TNF- α), interleukin (IL)-1b, IL-6, IL-12 and IL-10^[12]. In addition, these cells partake in the fibrogenetic process by inducing the secretion of transforming growth factor- β (TGF- β), platelet-derived growth factor (PDGF), matrix metalloproteinases, and reactive oxygen species (ROS)^[8].

Hepatocytes

TLRs 2, 3, 4, and 5 are expressed in low amounts, in contrast to Kupffer cells, on hepatocytes where they function to capture and remove endotoxins introduced into the liver from portal, as well as hepatic, circulation. In addition, stimulation of TLRs by their ligands results in induction of a pro-inflammatory cytokine response, albeit much less defined than that observed with Kupffer cells^[12].

Hepatic stellate cells

TLRs 4 and 9 are expressed on hepatic stellate cells where they cause chemokine and adhesion molecule upregulation. In addition, stimulation of TLR4 also promotes signaling of transforming growth factor- β (TGF- β) and induction of fibrogenesis while participating in cell defense through the TLR4-MyD88-mediated inflammatory response upon exposure to LPS^[6,9,12,13]. As a result, single nucleotide polymorphisms (SNPs) of TLR4 are associated with enhanced risk of fibrosis progression in patients with chronic HCV infection^[13], and offer an approach to recognize fibrosis risk genes^[14-16].

Biliary epithelial cells

These cells express TLRs 2, 3, 4, and 5, of which TLR 2 and 4 stimulation leads to upregulation of interleukin-1 receptor-associated kinase (IRAK) with resultant tolerance to LPS, a particularly important host protection mechanism against uncontrolled TLR signaling brought about by the activation of biliary epithelial cells specific pathogen-related molecular arrangement located in the intestinal lumen^[17].

Other hepatic cells

Stimulation of TLR4 expressed on liver sinusoidal endothelial cells activates a nuclear factor kappa β (NF κ B) dependent pathway resulting in secretion of TNF- α and reactive oxygen species^[18], while hepatic dendritic cells (DCs), the primary antigen presenting cells (APCs) of the liver, primary sources of interferon α (IFN- α) released in response to ligand-induced stimulation of TLRs 4, 7, and 9^[19].

POST ORTHOTOPIC LIVER TRANSPLANTATION INFECTIONS

While orthotopic liver transplantation is often lifesaving in many instances, death following this procedure is most commonly due to infection that occurs in up to 80% of transplant recipients, most commonly due to microbial causes in up to 70% of cases with viral infections coming second at 20% and fungal infections affecting only a minority of cases at 8% (Table 1)^[20]. Risk of infection to recipients of liver transplantation is reliant on strength of the infectious agent in conjunction with host immune state^[21], as evidenced by the increased likelihood of patients with patients with end-stage liver disease (ESLD) acquiring infections due to associated conditions of defective immunity, including neutropenia, weakness of the mucocutaneous wall, occurrence of necrotic tissue, ischemia, and diabetes mellitus^[22].

Post-transplant infection occurs from a number of different sources including de novo infection or recurrence of infection in the recipient patient, transplantation of infected graft, and nosocomial infection during hospital stay. Cause of the infection may be ascertained from the period directly following the transplant. The immunosuppressive state of these patients is dependent on the amount, type, and duration of the immunosuppressive agent used^[21].

Table 1 Types of infections after orthotopic liver transplantation

	First month post transplant	1-6 mo post transplant	> 6 mo post transplant
Bacterial infections	<i>Staph aureus</i> , <i>Streptococci enterococci</i> , <i>Salmonella pseudomonas</i> , MRSA, VRE, <i>Aerobes</i> , <i>Clostridium difficile</i>	Multidrug resistant bacteria, <i>Listeria spp</i>	Multidrug resistant bacteria
Viral	Human herpes virus 6	CMV, HCV, EBV, VZV	HHV8, HEV, EBV, Parvovirus B19
Fungal	<i>Candida</i> , <i>Asprgillus</i>	Mucormucosis, Pneumocystitis jirovicii (PJP)	<i>Nocardia</i> , <i>Rhodococcus</i> , <i>Legionella</i> , <i>Cryptococcus</i> , Blastomycosis, histoplasmosis
Mycobacterial		TB	TB, Non tuberculous <i>Mycobacteria</i> (Mycobacterial avium complex, Myco. triplex)
Protozoal			Strongyloidosis, toxoplasmosis; Echinococcosis, Chagas disease
Types of infections	Wound infections, Abdominal infections, catheter related infections, pneumonia, UTL, abscess, cholangitis, peritonitis	Community acquired infections, Invasive fungal infection	Community acquired pathogens, Opportunistic infections

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HEV: Hepatitis E virus; HHV: Human herpes virus; HIV: Human immune deficiency virus; HSV: Herpes simplex virus; MRSA: Methicillin-resistant *Staphylococcus aureus*; VRE: Vancomycin-resistant *Enterococcus*; VZV: Varicella zoster virus.

RISK FACTORS FOR INFECTION FOLLOWING LIVER TRANSPLANTATION

Recipients of orthotopic liver transplantation become more susceptible to infective agents in situations of present underlying causative, immunosuppressive state of the recipient with regards to type of immunosuppressive drug administered and the extent of the disease, technical complications during the transplant procedure, and exposure to pathogens within the hospital and public environment^[23].

TLRS AND INFECTION AFTER LIVER TRANSPLANTATION

TLRs and infectious liver diseases

Pathophysiology of a number of infectious diseases, including *Listeria*, *Salmonella*, and the *Plasmodium* species, is affected by TLRs. Following the invasion of hepatic tissue, *Listeria monocytogenes* replicates in hepatocytes and Kupffer cells, prompting the infected Kupffer cells to subsequently initiate a counterattack through a TLR2/MyD88-dependent pathway to secrete of the pro-inflammatory cytokines tumour necrosis factor- α (TNF- α) and interleukin-12. While this extensive pro-inflammatory release of cytokines in response to *L. monocytogenes* infection is defective in MyD88-deficient rats, giving rise to a higher rate of mortality^[12], TLR2-deficient mice show normal clearance of the infection in spite of a diminished cytokine response. This suggests that although TLR2 does participate in the cytokine cascade, clearance of *L. monocytogenes* is dependent on a number of collaborating TLRs^[24].

Infection with *Salmonella typhimurium* is typically cleared by Kupffer cells in the liver through an antimicrobial response involving TLR4 and nitric oxide, consequently leading to granuloma formation^[25], while infection with *Salmonella choleraesuis* results in liver injury by induction of TLR2-mediated upregulation of Fas-ligand on natural killer cells^[26]. In spite of these TLRs playing a major role in the pathogenesis of *Salmonella*, elimination of *S. choleraesuis* does not depend on the actions of TLR2 and TLR4, as intracellular growth of this pathogen had diminished on activation of TLR9, suggesting that eradication of *Salmonella* is also dependent on several TLRs^[27].

Malaria causes liver injury in humans by infection with *Plasmodium falciparum* and in mice by *Plasmodium berghei* through a TLR/MyDD88-mediated pathway leading to lymphocytic infiltration and subsequent death of hepatocytes^[28]. Variants of TLRs 1 and 6 were found to be associated with milder forms of malaria, while TLR9 (1486 C/T) variant was more likely related to higher levels of malarial parasitemia^[29].

Other SNPs of TLRs have also been associated with increased likelihood of infection. SNP of TLR2 (R753Q), resulting in impaired TLR2 signaling, has been associated with increased susceptibility to tuberculosis infection in a Turkish study^[30],

while a Tunisian study reported that tuberculosis patients demonstrated higher frequency of TLR2 (Arg677Trp) polymorphism than healthy control subjects, suggesting that presence of this polymorphism was a risk factor for pulmonary tuberculosis^[31]. This finding was contradicted, however, in another study showing that TLR2 (Arg677Trp) polymorphism did not convey risk to tuberculosis in a population of Iranian and Indian subjects^[32].

TLR signaling and HCV recurrence following liver transplantation

The probability of acquiring infection following hepatic transplantation is heightened due to affection of the innate immune defense mechanisms of the host following this procedure. That said, recurrence of HCV infection after liver transplantation (LT) is a universal occurrence, with the course of infection being greatly accelerated when compared to infection outside of the transplant setting^[33].

TLR2 signaling pathway plays a major role in recurrence of HCV following liver transplantation. Homozygosity of TLR2 (Arg753Gln) polymorphism has been associated with higher mean fibrosis levels as well as higher graft cirrhosis and loss, leading to higher mortality of HCV cases post-transplantation. On the other hand, SNPs of TLR4 (Asp299Gly) and (Thr399Ile) showed no association with any serious complications following liver transplantation^[34]. However, TLR2 (R753Q) SNP has been reported to hinder immune recognition of HCV core and NS3 proteins that is reliant on TLR2, possibly explaining why allograft failure develops in patients with chronic hepatitis C who undergo liver transplantation^[35].

Abnormal blood mononuclear cell secretion of interferon- α and NK CD56dim cell secretion of interferon- γ due to impaired TLR7/8-mediated pathway are associated with more aggressive post-transplantation recurrence of HCV infection in comparison to slower course HCV infections following liver transplantation^[36]. Furthermore, patients demonstrating rapid progression of fibrosis show impaired blood mononuclear cell secretion of tumour necrosis factor- α (TNF- α) and interleukin-6 both at baseline and with TLR3 receptor stimulation. TLR3 receptors are functional receptors expressed on monocytes where they are dominant initiators of host antiviral responses^[37-39]. Therefore, it is reasonable to assume that hindered secretion of TLR3-mediated monocyte-derived TNF- α and interleukin-6 results in impaired NK and dendritic cell stimulation leading to increased fibrosis^[36].

Natural killer CD56 dim cells secrete IFN- γ that stimulates dendritic cells and T cells, thereby aiding Th1 anti-viral cytokine responses. Impairment of this secretory release promotes Th2 rather than Th1 cytokine response^[40,41], leading to impaired HCV-directed T cell response, particularly with regards to CD4⁺T cell protection against progression of liver disease^[42]. Rapid progression of fibrosis in HCV patients is attributed to inadequate viral control by the immune system^[43,44], leading to heightened production of pro-inflammatory cytokines with increased stimulation of pro-fibrogenic pathways^[15,45,46].

Secretion of interferon- α and interferon- γ has been shown to be extremely important in host viral defense mechanisms, with emphasis on the fundamental role of TLR7/8 signaling pathways in recurrence of HCV infection post-LT. This consideration becomes even more eminent when coupled with data demonstrating the negative effect of calcineurin inhibitors on TLR7/8-mediated human NK CD56dim cell secretion of interferon- γ in patients having undergone liver transplantation^[36,47].

Polymorphism of TLR2 and infections with Gram-positive bacteria after liver transplantation

It is generally accepted that cell wall components of Gram-positive bacteria, particularly peptidoglycan and lipoteichoic acid, are recognized by TLR2^[48]. SNPs in certain TLR genes have been reported to negatively impact responses of these receptors to their corresponding ligands^[35]. TLR2 (R753Q) SNP, caused by substitution of arginine for glutamine at position 753, was shown to result in defective intracellular signaling resulting in modification of cytokine secretion in response to stimulation by peptidoglycan, lipopeptides, and other bacterial components leading to increased susceptibility to bacterial infections^[35]. In addition, this SNP showed high association with Gram-positive septic shock infections and staphylococcal infections^[49].

Similarly, cell membrane constituents of *S. aureus* did not elicit TNF- α response from TLR2-deficient macrophages^[50]. Compared with wild-type rats, those with TLR2-deficiency showed increased susceptibility to infection with *S. aureus*. These TLR2-deficient rats demonstrated increased mortality rates of 80% on day 8 and 90% on day 14 after being subjected to experimentally high infectious doses *S. aureus*, compared to rates of 0% and 40%, respectively, in wild-type rats. Moreover, cirrhotic patients have been shown to demonstrate increased susceptibility to spontaneous bacterial peritonitis with presence of the variant SNP TLR2 (R753Q)^[50,51].

Nevertheless, post-transplantation susceptibility to infection in patients with TLR2 (Arg753Gln) polymorphism remains inconclusive, with one study showing no association of this SNP with infections of viral or fungal nature following transplantation of allogeneic stem cells, although there has been an association between TLR2 (Arg753Gln) SNP and CMV infection and replication post-LT^[52]. However, other reports provide conflicting results, revealing that prevalence of this SNP was not increased in patients with Gram-positive bacteremia^[53], a difference that may be attributed to the variation in patient sample as this study included cases of HIV infection, Gram-positive bacterial infections, and septic shock^[53,54]. Another study evaluating *S. aureus* infection of prosthetic joints demonstrated that frequency of TLR2 (R753Q) SNP was relatively similar between infected patients and controls, with the likelihood of developing complications of *S. aureus* infection was basically similar between patients with wild-type TLR2 gene and those with polymorphism^[55]. Furthermore, no association could be ascertained between aggressive *S. aureus* infection and presence of mutant TLR2 (R753Q) SNP^[56]. A lack of difference in TLR2 (R753Q) SNP between patients with and without Gram-positive infections has also been reported, these infections found in transplant patients with TLR2 (R753Q) SNP in similar frequencies as in those with wild-type gene^[57].

While these results appear to propose a lack of significant impact of TLR2 in human infection, other data has suggested the contrary. The same study by Lee *et al.*^[57] also reported that TLR2 (R753Q) SNP showed marked association with increased risk of septic shock, in addition to a relatively insignificant tendency towards risk of recurring infection. However, no significant relationship could be determined between TLR2 (R753Q) SNP and 90-d all-cause death. This can be partly attributed to presence of other receptors playing a role in pathogen recognition, such as identification of Gram-positive infections through the nucleotide oligodimerization domain^[58]. Similarly, infection with *S. aureus* in an animal model is recognized by several types of TLRs, including TLR2^[59]. Another explanation for the apparent clinical irrelevance between TLR2 and infection may be the dose of infectious pathogen, as TLR2 and survival from *S. aureus* infection were found to be correlated only in cases of infections with large dose of pathogen^[50].

Relationship between polymorphism of TLR2 and infection with cytomegalovirus following liver transplantation

The report of TLR2 (R753Q) SNP inhibiting TLR2 signaling on exposure to cytomegalovirus glycoprotein B may provide the basis for association of this polymorphism with human cytomegalovirus disease^[59]. Homozygosity of TLR2 (Arg753Gln) SNP has been reported to be associated with high incidence of CMV infection post-transplantation of liver and the kidney^[60,61], in addition to indicating risk for CMV infection, especially tissue-invasive type, following liver transplantation^[62].

TLRs have been reported to take part in the innate defense mechanisms against infection with CMV, with CMV-induced activation of TLR2 resulting in production of cytokines via a nuclear factor kappa B (NFκB)-mediated pathway^[63]. TLR2(Arg753Gln) SNP requires presence of only a single functional wild-type allele to control CMV infection, as cells with heterozygosity for this polymorphism function similarly as those with wild-type gene, having the capability to respond on activation with TLR2 agonist^[64]. Conversely, cases with homozygosity for TLR2 (Arg753Gln) SNP show replication of cytomegalovirus and manifest clinical disease. However, it should be noted that CMV disease is less manifest in cases with heterozygosity for this SNP, in spite of the fact that viral replication is more pronounced^[60].

Effects of Cyclosporine and Tacrolimus on TLR signaling after liver transplantation

The deficient peripheral blood mononuclear cell (PBMC) pro-inflammatory cytokine secretion observed on stimulation of TLRs 2, 4, and 7/8 on administration of tacrolimus and cyclosporine therapy in patients when compared to healthy control subjects suggests a class effect for calcineurin inhibitors on function of these TLRs. However, examination by flowcytometry demonstrated that no specific individual cell subtype could be identified as accountable for the functional modification of these receptors, suggesting that the suppressive effect of calcineurin inhibitors on TLRs 2, 4, and 7/8 is apparent in PBMCs but variable in individual cell subtypes^[65].

Similarly, calcineurin inhibitors have also been shown to down-regulate TLR4 stimulated by lipopolysaccharides, although pre-treatment of cells with tacrolimus resulted in diminished inflammatory response to lipopolysaccharides, suggesting initiation of lipopolysaccharide intolerance (73). Impaired secretion of tumor necrosis factor-α (TNF-α) and interleukin-6 mediated through TLRs 2, 4, and 7/8 pathways has been demonstrated from PBMCs cultured with both TLR agonist and calcineurin inhibitors when compared with controls^[65].

CONCLUSION

The liver is the first host defensive structure against the bacteria and bacterial products that are persistently received from the gut by way of the portal circulation. However, this massive influx of gut bacteria does not elicit an inflammatory reaction in healthy individuals due to tolerance of the abundantly present TLRs on the surface of hepatic cells. While orthotopic liver transplantation is often lifesaving in many instances, death following this procedure is most commonly due to infection that occurs in up to 80% of transplant recipients. SNPs in certain *TLR* genes have been associated with increased susceptibility to infections (Table 2). SNPs of TLR2 have been associated with both Gram-positive and Gram-negative bacteria (e.g., *Listeria*, *Salmonella*), *Mycobacterium tuberculosis* and the *Plasmodium* species, in addition to CMV infection and the universal recurrence of HCV following liver transplantation. Similarly, impaired TLR7/8-mediated pathway has been associated with more aggressive post-transplantation recurrence of HCV infection, while reports on TLR3 polymorphism have demonstrated comparable results.

Our hypothesis is that *TLR* genes and their proteins have influence in the outcome of post liver transplantation infection. This risk factor are responsible for mortality rate of liver transplant. Understanding the genetic variation of *TLR* gene in liver transplant may clarify the underlying mechanisms behind the post-transplant infection. It may also enables the development of early diagnostic tests for predication of either the persistence or clearance of infection. Genetic study may be also open some windows for new treatments, or interventions to prevent disease onset or minimize disease severity.

Association between TLRs genotypes and post transplant infection have traditionally been studied by determining the genotype of known markers. However, these associations studies of single gene typically explain less than 25% of the heritable risk estimated for each of those diseases. Furthermore, the heterogeneity, ethnic variation and complex relationship between genotype and phenotype may also difficult, to predict which genes are most likely to be implicated as a candidate gene for a particular outcome. We recommended several approaches to investigate the association of *TLR* (1-10) genes with the outcome of post-transplant infection. These approaches include: (1) Genome wide association study (GWAS) using next-generation sequencing techniques (NGS) for the whole genome to identify the entire underlying genetic variation and its disease relevance. Applying NGS to GWAS will help for better identification of candidate genes in a short time, and in an efficient way. (2) Gene expression epigenetic analyses of *TLR* gene may also provide more information about the underlying mechanism of these factors for the disease outcome. (3) Furthermore, correlation study of different genotype with serum levels of cytokine net levels are also required. And (4) Multicentric well-designed studies of large sample size are needed to avoid false negative results that may arise from under-evaluation of interactions involving gene-to-gene relations or gene environment among different ethnic populations.

Limitations of the study

The major limitation of this article is the study design, as it is a narrative review article. It is well known that narrative review articles are more susceptible to selection bias and this may affect its conclusion. Systematic review articles adhere to strict methodology, thus are, potentially, more reliable scientifically.

Table 2 Association of Toll-like receptors alleles with infections post liver transplantation and their clinical significance

Type of Infection	Type of organism	TLR alleles	Clinical significance
Bacterial infections	Staph aureus	TLR2 (Arg753Gln)	Inconclusive association with septic shock
		TLR2 (R753Q)	May correlated only in cases of infections with large dose of pathogen
	<i>Listeria monocytogenes</i>	TLR2/MyD88-dependent pathway	Participate in cytokine cascade No role in clearance
	<i>Salmonella typhimurium</i>	TLR4	Granuloma formation
	<i>Salmonella choleraesuis</i>	TLR2, TLR4	Have role in pathogenesis; No role in clearance
Protozoal	<i>Plasmodium falciparum</i>	TLR9	Has role in clearance
		TLR1, TLR6	Mild form of malaria
Mycobacterium	Mycobacterial tuberculosis	TLR9 (1486 C/T)	Severe form of malaria
		TLR2 (R753Q)	Increased susceptibility to T.B in Turkish
Viral	Hepatitis C virus (HCV)	TLR2 (Arg677Trp)	Increased susceptibility to T.B in Tunisian but not to Iranian and Indian populations.
		TLR2 (Arg753Gln)	Recurrence of HCV post transplant (PT) with higher graft cirrhosis and graft failure
		TLR2 (R753Q)	Higher rate of graft failure
		TLR3	Increased liver fibrosis
	Cytomegalovirus (CMV)	TLR4 (Asp299Gly) and (Thr399Ile)	No associated PT complications
		TLR7/8-mediated pathway	Aggressive PT recurrence of HCV
		TLR2 (R753Q) TLR2 (Arg753Gln)	Increased incidence of CMV PT

TLR: Toll-like receptor.

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